(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/22919 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US00/26387

(22) International Filing Date:
26 September 2000 (26.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/157,207 30 September 1999 (30.09.1999) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **HOFFMAN, Jacob, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/22919 A2

(54) **Title:** SPIRO[BICYCLIC -AZACYCLOALKYL AND -CYCLOALKYL] DERIVATIVES AND USES THEREOF

(57) **Abstract:** Spiro[bicyclic -azacycloalkyl and -cycloalkyl] derivatives and their pharmaceutically acceptable salts are disclosed. The synthesis of these compounds and their use as alpha 1a adrenergic receptor antagonists is also described. One application of these compounds is in the treatment of benign prostatic hyperplasia. These compounds are typically selective in their ability to relax smooth muscle tissue enriched in the alpha 1a receptor subtype without at the same time inducing hypotension. One such tissue is found surrounding the urethral lining. Therefore, one utility of the instant compounds is to provide acute relief to males suffering from benign prostatic hyperplasia, by permitting less hindered urine flow. Another utility of the instant compounds is provided by combination with a human 5-alpha reductase inhibitory compound, such that both acute and chronic relief from the effects of benign prostatic hyperplasia can be achieved.

TITLE OF THE INVENTION

SPIRO[BICYCLIC -AZACYCLOALKYL AND -CYCLOALKYL] DERIVATIVES AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to spiro[bicyclic -azacycloalkyl and -cycloalkyl] derivatives and pharmaceutically acceptable salts thereof, their synthesis, and their use as alpha 1a adrenoceptor antagonists. The spirobicyclic derivatives of present invention include, but are not limited to, compounds having oxazolidinone, thiazolidinone, dihydropyridimidinone, and saccharin moieties attached to the spirobicyclic ring systems via alkyl, alkylaminocarbonyl, and cycloalkylaminocarbonyl linkers. The compounds of the present invention are useful for treating benign prostatic hyperplasia (BPH).

References are made throughout this application to various publications, the disclosures of which are hereby incorporated by reference in their entireties, in order to more fully describe the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

Human adrenergic receptors are integral membrane proteins which have been classified into two broad classes, the alpha and the beta adrenergic receptors. Both types mediate the action of the peripheral sympathetic nervous system upon binding of catecholamines, norepinephrine and epinephrine.

Norepinephrine is produced by adrenergic nerve endings, while epinephrine is produced by the adrenal medulla. The binding affinity of adrenergic receptors for these compounds forms one basis of the classification: alpha receptors bind norepinephrine more strongly than epinephrine and much more strongly than the synthetic compound isoproterenol. The binding affinity of these hormones is reversed for the beta receptors. In many tissues, the functional responses, such as smooth muscle contraction, induced by alpha receptor activation are opposed to responses induced by beta receptor binding.

Subsequently, the functional distinction between alpha and beta receptors was further highlighted and refined by the pharmacological characterization of these receptors from various animal and tissue sources. As a result, alpha and beta adrenergic receptors were further subdivided into alpha 1, alpha 2, β_1, and β_2

subtypes. Functional differences between alpha 1 and alpha 2 receptors have been recognized, and compounds which exhibit selective binding between these two subtypes have been developed.

For a general background on the alpha adrenergic receptors, the reader's attention is directed to Robert R. Ruffolo, Jr., α-Adrenoreceptors: Molecular Biology, Biochemistry and Pharmacology, (Progress in Basic and Clinical Pharmacology series, Karger, 1991), wherein the basis of alpha 1/alpha 2 subclassification, the molecular biology, signal transduction (G-protein interaction and location of the significant site for this and ligand binding activity away from the 3'-terminus of alpha adrenergic receptors), agonist structure-activity relationships, receptor functions, and therapeutic applications for compounds exhibiting alpha-adrenergic receptor affinity was explored.

The cloning, sequencing and expression of alpha receptor subtypes from animal tissues has led to the subclassification of the alpha 1 receptors into alpha 1d (formerly known as alpha 1a or 1a/1d), alpha 1b and alpha 1a (formerly known as alpha 1c) subtypes. Each alpha 1 receptor subtype exhibits its own pharmacologic and tissue specificities. The designation "alpha 1a" is the appellation recently approved by the IUPHAR Nomenclature Committee for the previously designated "alpha 1c" cloned subtype as outlined in the 1995 Receptor and Ion Channel Nomenclature Supplement (Watson and Girdlestone, 1995). The designation alpha 1a is used throughout this application to refer to this subtype. At the same time, the receptor formerly designated alpha 1a was renamed alpha 1d. The new nomenclature is used throughout this application. Stable cell lines expressing these alpha 1 receptor subtypes are referred to herein; however, these cell lines were deposited with the American Type Culture Collection (ATCC) under the old nomenclature. For a review of the classification of alpha 1 adrenoceptor subtypes, *see*, Michel et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* (1995), 352: 1-10.

The differences in the alpha adrenergic receptor subtypes have relevance in pathophysiologic conditions. Benign prostatic hyperplasia, also known as benign prostatic hypertrophy or BPH, is an illness typically affecting men over fifty years of age, increasing in severity with increasing age. The symptoms of the condition include, but are not limited to, increased difficulty in urination and sexual dysfunction. These symptoms are induced by enlargement, or hyperplasia, of the prostate gland. As the prostate increases in size, it impinges on free-flow of fluids through the male urethra. Concommitantly, the increased noradrenergic innervation

of the enlarged prostate leads to an increased adrenergic tone of the bladder neck and urethra, further restricting the flow of urine through the urethra.

In benign prostatic hyperplasia, the male hormone 5alpha-dihydrotestosterone has been identified as the principal culprit. The continual production of 5α-dihydrotestosterone by the male testes induces incremental growth of the prostate gland throughout the life of the male. Beyond the age of about fifty years, in many men, this enlarged gland begins to obstruct the urethra with the pathologic symptoms noted above.

The elucidation of the mechanism summarized above has resulted in the recent development of effective agents to control, and in many cases reverse, the pernicious advance of BPH. In the forefront of these agents is Merck & Co., Inc.'s product PROSCAR® (finasteride). The effect of this compound is to inhibit the enzyme testosterone 5-α reductase, which converts testosterone into 5α-dihydrotesterone, resulting in a reduced rate of prostatic enlargement, and often reduction in prostatic mass.

The development of such agents as PROSCAR® bodes well for the long-term control of BPH. However, as may be appreciated from the lengthy development of the syndrome, its reversal also is not immediate. In the interim, those males suffering with BPH continue to suffer, and may in fact lose hope that the agents are working sufficiently rapidly.

In response to this problem, one solution is to identify pharmaceutically active compounds which complement slower-acting therapeutics by providing acute relief. Agents which induce relaxation of the lower urinary tract tissue, by binding to alpha 1 adrenergic receptors, thus reducing the increased adrenergic tone due to the disease, would be good candidates for this activity. Thus, one such agent is alfuzosin, which is reported in EP 0 204597 to induce urination in cases of prostatic hyperplasia. Likewise, in WO 92/00073, the selective ability of the R(+) enantiomer of terazosin to bind to adrenergic receptors of the alpha 1 subtype was reported. In addition, in WO 92/16213, combinations of 5α reductase inhibitory compounds and alpha1-adrenergic receptor blockers (terazosin, doxazosin, prazosin, bunazosin, indoramin, alfuzosin) were disclosed. However, no information as to the alpha 1d, alpha 1b, or alpha 1a subtype specificity of these compounds was provided as this data and its relevancy to the treatment of BPH was not known. Current therapy for BPH uses existing non-selective alpha 1 antagonists such as prazosin (Minipress, Pfizer), Terazosin (Hytrin, Abbott) or doxazosin mesylate (Cardura, Pfizer). These

non-selective antagonists suffer from side effects related to antagonism of the alpha 1d and alpha 1b receptors in the peripheral vasculature, e.g., hypotension and syncope.

The relatively recent cloning of the human alpha 1a adrenergic receptor (ATCC CRL 11140) and the use of a screening assay utilizing the cloned human alpha 1a receptor has enabled identification of compounds which specifically interact with the human alpha 1a adrenergic receptor. For further description, see WO 94/08040 and WO 94/10989. As disclosed in the instant patent disclosure, a cloned human alpha 1a adrenergic receptor and a method for identifying compounds which bind the human alpha 1a receptor have made possible the identification of selective human alpha 1a adrenergic receptor antagonists useful for treating BPH.

Several classes of compounds have been disclosed to be selective alpha 1a adrenergic receptor antagonists useful for treating BPH. WO 94/22829 discloses, for example, certain 4-(un)substituted phenyl-1,4-dihydropyridine derivatives which are described as potent, selective alpha 1a antagonists with weak calcium channel antagonistic activity and which are further described to be anticipated as useful for treating BPH. As another example, WO 96/14846, WO 97/17969 and WO 97/42956 each disclose certain dihydropyrimidine derivatives (e.g., certain 1,2,3,6-tetrahydro-2-oxo-pyrimidine derivatives) which are selective antagonists for the human alpha 1a receptor and useful for treatment of BPH, impotency, cardiac arrhythmia, and other diseases where antagonism of the alpha 1a receptor may be useful. As still another example, WO 96/40135 discloses, *inter alia*, certain phenylpiperidinyl alkyl saccharin derivatives and their use as selective alpha 1a antagonists. Yet another example is EP 748800, which discloses, *inter alia*, certain arylpiperazinylpropyl substituted pyrimidinediones useful as alpha 1 adrenoceptor antagonists. Still other alpha 1a selective antagonist compounds are disclosed in WO 98/57632, WO 98/57638, WO 98/57639, WO 98/57640, WO 98/57641, WO 98/57642, and WO 98/57940.

Yet another example is US 5760054, which describes certain butyl saccharin derivatives, including certain piperidinyl benzoxazine-substituted and spiroindanyl piperidine-substituted butyl saccharins. US '054 also discloses the use of these derivatives as selective alpha 1a adrenergic receptor antagonists.

Still another example is WO 98/51311, which discloses certain dihydropyrimidine derivatives including derivatives that have certain spirobicyclic piperdine substituents. See, for example, pages 11 and 12 of WO '311.

The instant patent specification discloses novel spiro[bicyclic - azacycloalkyl and -cycloalkyl] derivatives which bind to the human alpha 1a receptor.

These compounds are further tested for binding to other human alpha 1 receptor subtypes, as well as counterscreened against other types of receptors (e.g., alpha 2), thus defining the specificity of the compounds of the present invention for the human alpha 1a adrenergic receptor.

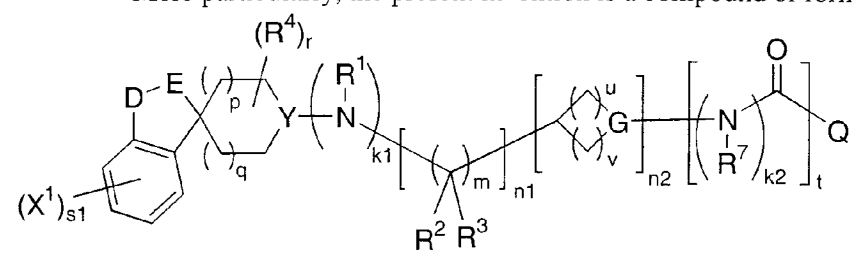
It is an object of the present invention to identify compounds which bind to the alpha 1a adrenergic receptor. It is a further object of the invention to identify compounds which act as antagonists of the alpha 1a adrenergic receptor. It is another object of the invention to identify alpha 1a adrenergic receptor antagonist compounds which are useful agents for treating BPH in animals, preferably mammals, especially humans. Still another object of the invention is to identify alpha 1a adrenergic receptor antagonists which are useful for relaxing lower urinary tract tissue in animals, preferably mammals, especially humans.

The compounds of the present invention are alpha 1a adrenergic receptor antagonists. Thus, the compounds of the present invention are useful for treating BPH in mammals. Additionally, it has been found that the alpha 1a adrenergic receptor antagonists of the present invention are also useful for relaxing lower urinary tract tissue in mammals.

SUMMARY OF THE INVENTION

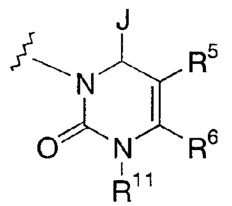
The present invention provides spiro[bicyclic -azacycloalkyl and -cycloalkyl] derivatives and pharmaceutically acceptable salts thereof for the treatment of urinary obstruction caused by benign prostatic hyperplasia (BPH). The compounds antagonize the human alpha 1a adrenergic receptor at nanomolar and subnanomolar concentrations, while exhibiting lower affinity for the alpha 1d and alpha 1b human adrenergic receptors and many other G-protein coupled receptors. This invention can have the advantage over non-selective alpha 1 adrenoceptor antagonists of reduced side effects related to peripheral adrenergic blockade. Such side effects include hypotension, syncope, lethargy, etc.

More particularly, the present invention is a compound of formula (I):

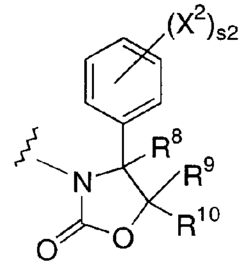


(I) ;

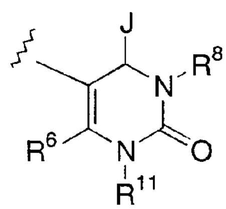
wherein Q is



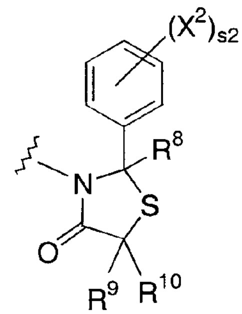
(q1),



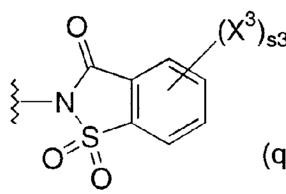
(q2),



(q3),



(q4), or



(q5) ;

D is absent, $[C(R^aR^b)]_{1\text{-}4}$, $O[C(R^aR^b)]_{1\text{-}2}$, $[C(R^aR^b)]_{1\text{-}2}O$, $C(R^a)=C(R^b)$, $C(R^aR^b)\text{-}C(R^a)=C(R^b)$, or $C(R^a)=C(R^b)\text{-}C(R^aR^b)$;

E is absent, C(=O), C(=O)O, $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$, or $N(R^c)C(=O)O$, provided that (i) when E is absent, D is $[C(R^aR^b)]_{2\text{-}4}$, $O[C(R^aR^b)]_{1\text{-}2}$, $[C(R^aR^b)]_{1\text{-}2}O$, $C(R^a)=C(R^b)$, $C(R^aR^b)\text{-}C(R^a)=C(R^b)$, or $C(R^a)=C(R^b)\text{-}C(R^aR^b)$; (ii) when E is C(=O) or C(=O)O, D is $C(R^aR^b)$ or $C(R^aR^b)C(R^aR^b)$; and (iii) when E is $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$ or $N(R^c)C(=O)O$, D is absent or $C(R^aR^b)$;

G is CH or N;

Y is CH or N;

k1 is an integer which is equal to zero when Y is N, and is equal to 1 when Y is CH;

k2 is an integer which is equal to zero when n2 is 1 and G is N, and is equal to 1 when (i) n2 is 1 and G is CH or (ii) n2 is zero;

m is an integer from 2 to 6;

n1 and n2 are each integers equal to zero or 1, with the proviso that the sum of n1 and n2 is 1 or 2;

p and q are each independently integers from zero to 3;

r is an integer from zero to 4;

R^1 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $(CH_2)_{1-4}CF_3$, $(CH_2)_{0-4}CO_2R^e$, $(CH_2)_{0-4}C(=O)N(R^e)_2$, $(CH_2)_{0-4}C(=O)R^e$, $(CH_2)_{2-4}OR^d$, $(CH_2)_{1-4}CF_3$, $(CH_2)_{0-4}SO_2R^e$, $(CH_2)_{0-4}SO_2N(R^e)_2$ or $(CH_2)_{1-4}CN$;

R^2 and R^3 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

each R^4 is a substituent connected to a ring atom other than spiro substituted carbon or Y and is independently hydrogen or C_1-C_4 alkyl;

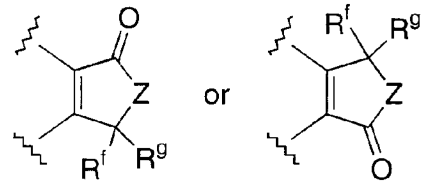
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $(CH_2)_{0-4}C(=O)R^d$, $(CH_2)_{0-4}CN$, $(CH_2)_{0-4}CF_3$, $(CH_2)_{0-4}CO_2R^e$, $(CH_2)_{0-4}C(=O)N(R^e)_2$, $(CH_2)_{0-4}SO_2R^d$ or $(CH_2)_{0-4}SO_2N(R^e)_2$;

R^6 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $(CH_2)_{1-4}OR^d$ or $(CH_2)_{0-4}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:

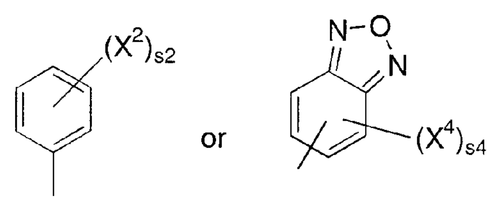


wherein Z is O or NR^f;

R^8 and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}4}CF_3$;

R^9 and R^{10} are each independently hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $(CH_2)_{2\text{-}4}OR^e$ or $(CH_2)_{0\text{-}4}CF_3$; or one of R^9 and R^{10} is hydrogen and the other of R^9 and R^{10} is $(CH_2)_{0\text{-}4}CO_2R^e$ or $(CH_2)_{0\text{-}4}C(=O)N(R^e)_2$;

J is



;

each X^1 is independently hydrogen, halogen, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_8 cycloalkyl, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{0\text{-}4}C(=O)N(R^h)_2$, C_1-C_6 alkoxy, fluorinated C_1-C_6 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_8 cycloalkyl, $(CH_2)_{0\text{-}4}CO_2R^h$,

$(CH_2)_{0-4}C(=O)N(R^h)_2$, C_1-C_6 alkoxy, fluorinated C_1-C_6 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl;

each X^3 is independently hydrogen, halogen, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_8 cycloalkyl, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{0-4}C(=O)N(R^h)_2$, C_1-C_6 alkoxy, fluorinated C_1-C_6 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl;

each X^4 is independently hydrogen, halogen, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_8 cycloalkyl, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{0-4}C(=O)N(R^h)_2$, C_1-C_6 alkoxy, fluorinated C_1-C_6 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl;

R^a and R^b are each independently hydrogen, C_1-C_4 alkyl, or fluorinated C_1-C_4 alkyl;

R^c is hydrogen, C_1-C_4 alkyl, or fluorinated C_1-C_4 alkyl;

R^d is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or $(CH_2)_{0-4}CF_3$;

R^e is hydrogen, C_1-C_6 alkyl, C_4-C_8 cycloalkyl, or $(CH_2)_{1-4}CF_3$;

R^f and R^g are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

R^h is hydrogen, C_1-C_4 alkyl, or fluorinated C_1-C_4 alkyl;

s1 is an integer from zero to 4;

s2 is an integer from zero to 5;

s3 is an integer from zero to 4;

s4 is an integer from zero to 3;

t is an integer which is zero or 1; and

u and v are independently integers from 1 to 3;

and further provided that

(i) when Q is (q1), k1 is zero, and n2 is zero, then (1) E is C(=O) and D = (R^aR^b), or (2) E is N(SO_2R^c)C(R^aR^b) or N(R^c)C(=O)O;

(ii) when Q is (q3), then t is 1;

(iii) when Q is (q5), then (1) t is zero and (2) G is CH when n2 is 1; and

(iv) when Q is (q1), (q2), or (q4), n2 is 1, and G is N, then t is 1;

or a pharmaceutically acceptable salt thereof.

The present invention also includes pharmaceutical compositions, methods of preparing pharmaceutical compositions, and methods of treatment.

These and other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes spirobicyclic derivatives of Formula (I) above. These compounds and their pharmaceutically acceptable salts are useful as alpha 1a antagonists.

A first embodiment of the present invention is a compound of Formula (I), wherein

p and q are each integers from zero to 3, provided that the sum of p and q is an integer less than or equal to 3;

r is an integer from zero to 2;

R^1 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or $(CH_2)_{1\text{-}4}CF_3$;

one of R^2 and R^3 is hydrogen and the other of R^2 and R^3 is hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

R^a and R^b are each independently hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0\text{-}4}CF_3$;

R^c is hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0\text{-}4}CF_3$;

R^d is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or $(CH_2)_{0\text{-}2}CF_3$;

R^e is hydrogen, C_1-C_4 alkyl, C_4-C_6 cycloalkyl, or $(CH_2)_{1\text{-}2}CF_3$;

R^f and R^g are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^h is hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0\text{-}4}CF_3$;

s1 is an integer from zero to 2;

s2 is an integer from zero to 3;

s3 is an integer from zero to 2;

s4 is an integer from zero to 2;

u is an integer from 1 to 2;

v is an integer from 1 to 3;

and all other variables are as originally defined above;

and further provided that

(i) when Q is (q1), k1 is zero, and n2 is zero, then (1) E is C(=O) and D is $C(R^aR^b)$ or (2) E is $N(SO_2R^c)C(R^aR^b)$ or $N(R^c)C(=O)O$;

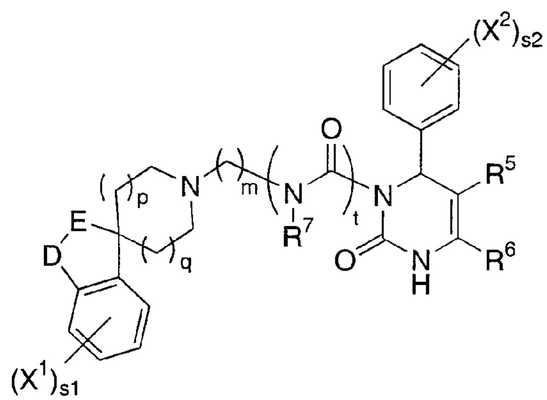
(ii) when Q is (q3), then t is 1;

(iii) when Q is (q5), then (1) t is zero and (2) G is CH when n2 is 1; and

(iv) when Q is (q1), (q2), or (q4), n2 is 1, and G is N, then t is 1;

or a pharmaceutically acceptable salt thereof.

A second embodiment of the present invention is a compound of Formula (II)



(II) ;

wherein

D is absent or [C(RaRb)];

E is C(=O), N(SO_2Rc)C(RaRb), or N(Rc)C(=O)O, provided that when E is C(=O), D is [C(RaRb)];

and all other variables are as defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

In an aspect of the second embodiment, E is N(SO_2Rc)C(RaRb) or N(Rc)C(=O)O.

A first class of the present invention is a compound of Formula (II), wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

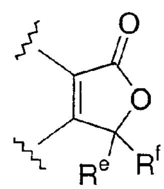
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $C(=O)R^d$, $(CH_2)_{0-2}CO_2R^e$, $(CH_2)_{0-2}C(=O)N(R^e)_2$, or SO_2R^d;

R^6 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{1-3}OR^d$ or $(CH_2)_{0-3}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:



;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

and all other variables are as described in the second embodiment;

or a pharmaceutically acceptable salt thereof.

Exemplary compounds of the preceding class are compounds selected from the group consisting of

(+/-)-1-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine ;

(+/-)-1-{5-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine ;

(+/-)-1-{[3-(6-Fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine ;

(+/-)-1-{5-(6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine ;

1-{[3-(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine ;

1-{[3-(1,2-dihydro-1-methanesulfonyl-6-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine ;

1-{[3-(2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine ;

1-{[3-(2,3-dihydro-3,3-dimethyl-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine ;

and pharmaceutically acceptable salts thereof.

A third embodiment of the present invention is a compound of Formula (I), wherein

Q is (q2);

Y is N;

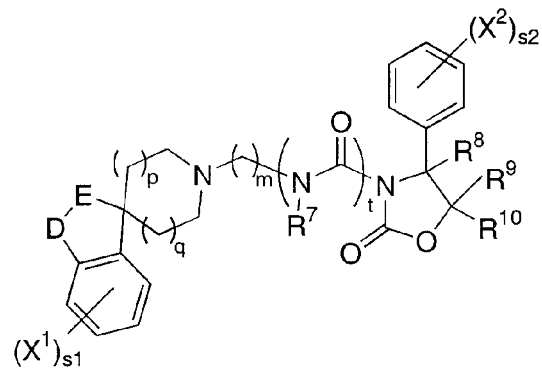
and all other variables are as defined in the first embodiment;

and further provided that when n2 is 1 and G is N, then t is 1;

or a pharmaceutically acceptable salt thereof.

An example of a compound embraced by this embodiment is 3-{[3(R/S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one , or a pharmacutically acceptable salt thereof.

A fourth embodiment of the present invention is a compound of Formula (III):



(III);

wherein all variables are as defined in the third embodiment;

or a pharmaceutically acceptable salt thereof.

A second class of the present invention is a compound of Formula (III), wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

R^8 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2-4}OR^d$ or $(CH_2)_{0-2}CF_3$;

R^9 and R^{10} are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2-4}OR^d$ or $(CH_2)_{0-2}CF_3$; or one of R^9 and R^{10} is hydrogen and the other of R^9 and R^{10} is CO_2R^e or $C(=O)N(R^e)_2$;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

and all other variables are as defined in the fourth embodiment;

or a pharmaceutically acceptable salt thereof.

Exemplary of compounds of the second class are compounds selected from the group consisting of

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one ;

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-5(S)-methoxycarbonyl-oxazolidin-2-one;

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-5(S)-aminocarbonyl-oxazolidin-2-one;

3-{[3-(spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

1-{[3-(5-monochloro-spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

1-{[3-(6-monochloro-spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(spiro[1H-indano-1,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(spiro[1H-indeno-1,4'-piperidin]-1'-yl)pentyl }-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

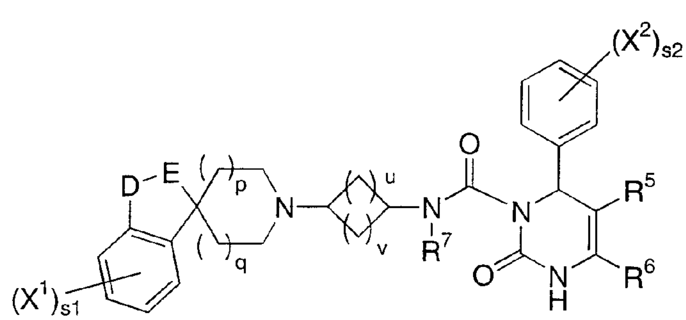
3-{[3-(6-chloro-spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(6-fluoro-spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

and pharmaceutically acceptable salts thereof.

A fifth embodiment of the present invention is a compond of Formula (IV):



(IV) ;

wherein all variables are as defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A third class of the present invention is a compound of Formula (IV), wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

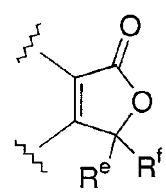
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $C(=O)R^d$, $(CH_2)_{0\text{-}2}CO_2R^e$, $(CH_2)_{0\text{-}2}C(=O)N(R^e)_2$, or SO_2R^d;

R^6 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{1\text{-}3}OR^d$ or $(CH_2)_{0\text{-}3}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:



;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

u and v are independently integers equal to 1 or 2;

and all other variables are as defined in the fifth embodiment;

or a pharmaceutically acceptable salt thereof.

Exemplary of compounds of the third class are compounds selected from the group consisting of

1-{*cis*-[3(S)-(spiro[indano-1,4'-piperidin]-1'-yl)cyclopent-1(R)-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{*trans*-[3(R)-(spiro[indano-1,4'-piperidin]-1'-yl)cyclopent-1(R)-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[*cis*-[3(S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclopent-1(R)-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[*trans*-[3(R)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclopent-1(R)-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

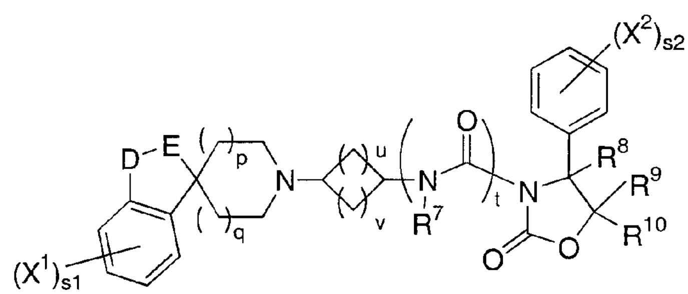
1-{[*cis*-3-(spiro[indano-1,4'-piperidin]-1'-yl)cyclobut-1-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[*trans*-3-(spiro[indano-1,4'-piperidin]-1'-yl)cyclobut-1-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[*trans*-4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclohex-1-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

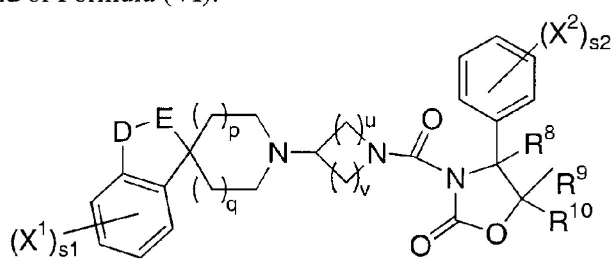
and pharmaceutically acceptable salts thereof.

A sixth embodiment of the present invention is a compound of Formula (V):



(V)

or a compound of Formula (VI):



(VI) ;

wherein all variables are as defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A fourth class of the invention is a compound of Formula (V) or Formula (VI), wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

R^8 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2-4}OR^d$ or $(CH_2)_{0-2}CF_3$;

R^9 and R^{10} are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2-4}OR^d$ or $(CH_2)_{0-2}CF_3$;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

and all other variables are as defined in the sixth embodiment;

or a pharmaceutically acceptable salt thereof.

Exemplary of compounds of the fourth class are compounds selected from the group consisting of

3-{[*cis*-3(S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[*trans*-3(R)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[*trans*-4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[*cis*-4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one ;

(3-{*trans*-4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl}- 4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one;

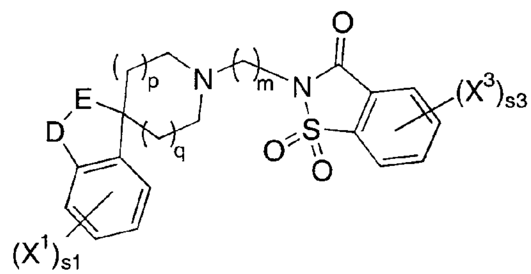
3-{[4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-piperidin-1-yl]carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{*cis/trans*-3(R/S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(S)-yl}- 4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{*cis/trans*-3(R/S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl}- 4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

and pharmaceutically acceptable salts thereof.

A seventh embodiment of the present invention is a compound of Formula (VII):



(VII) ;

wherein all variables are as defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A fifth class of the invention is a compound of Formula (VII), wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

each X^3 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

m is an integer equal to 4;

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

and all other variables are as defined in the seventh embodiment;

or a pharmaceutically acceptable salt thereof.

Exemplary of compounds of the fifth class are compounds selected from the group consisting of

1,1-dioxido-2-[4-(spiro[indano-1,4'-piperidin]-1'-yl)butyl]-5-chloro-1,2-benzisothiazol-3(2H)-one;

1,1-dioxido-2-[4-(2,3-dihydrospiro[1H-indeno-1,4'-piperidin]-2(3H)on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one;

1,1-dioxido-2-[4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one;

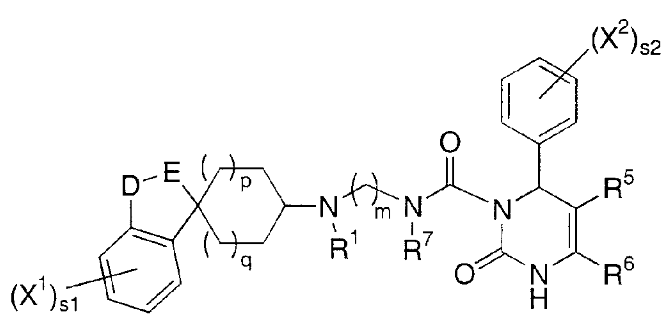
1,1-dioxido-2-[4-(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one;

1,1-dioxido-2-[4-(1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one;

1,1-dioxido-2-[4-(1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-5-chloro-1,2-benzisothiazol-3(2H)-one;

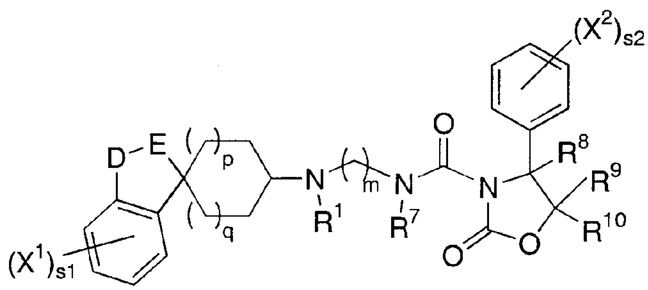
and pharmaceutically acceptable salts thereof.

An eighth embodiment of the present invention is a compound of Formula (VIII):



(VIII)

or a compound of Formula (IX):



(IX) ;

wherein

D is absent, $[C(R^aR^b)]_{1-4}$, $O[C(R^aR^b)]_{1-2}$, $[C(R^aR^b)]_{1-2}O$, $C(R^a)=C(R^b)$, $C(R^aR^b)-C(R^a)=C(R^b)$, or $C(R^a)=C(R^b)-C(R^aR^b)$;

E is absent, C(=O), C(=O)O, $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$, or $N(R^c)C(=O)O$, provided that (i) when E is absent, D is $[C(R^aR^b)]_{2-4}$, $O[C(R^aR^b)]_{1-2}$, $[C(R^aR^b)]_{1-2}O$, $C(R^a)=C(R^b)$, $C(R^aR^b)-C(R^a)=C(R^b)$, or $C(R^a)=C(R^b)-C(R^aR^b)$; (ii) when E is C(=O) or C(=O)O, D is $C(R^aR^b)$ or $C(R^aR^b)C(R^aR^b)$; and (iii) when E is $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$ or $N(R^c)C(=O)O$, D is absent or $C(R^aR^b)$;

and all other variables are as defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A sixth class of the invention is a compound of Formula (VIII) or a compound of Formula (IX), wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

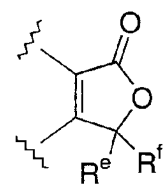
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $C(=O)R^d$, $(CH_2)_{0-2}CO_2R^e$, $(CH_2)_{0-2}C(=O)N(R^e)_2$, or SO_2R^d;

R^6 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{1\text{-}3}OR^d$ or $(CH_2)_{0\text{-}3}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:



;

R^8 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$;

R^9 and R^{10} are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$; and

m is an integer which is 2 or 3;

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

and all other variables are as defined in the eighth embodiment;

or a pharmaceutically acceptable salt thereof.

An aspect of the sixth class is a compound of Formula (VIII) or a compound of Formula (IX), wherein

D is absent or $[C(R^aR^b)]_{1\text{-}2}$;

E is C(=O), $N(SO_2R^c)C(R^aR^b)$, or $N(R^c)C(=O)O$, provided that when E is C(=O), D is $[C(R^aR^b)]_{1-2}$; and when E is $N(SO_2R^c)C(R^aR^b)$ or $N(R^c)C(=O)O$, D is absent or $C(R^aR^b)$;

and all other variables are as defined in the sixth class.

Exemplary of compounds in the sixth class are compounds selected from the group consisting of

3-{[2-(*cis*-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[2-(*trans*-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

1-{[2-(*cis*-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

and pharmaceutically acceptable salts thereof.

A preferred aspect of this invention is a compound selected from the group consisting of

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

1-{*cis*-[3(S)-(spiro[indano-1,4'-piperidin]-1'-yl)cyclopent-1(R)-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[3-(2,3-dihydro-3,3-dimethyl-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine;

1-{[3-(2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine;

and pharmaceutically acceptable salts thereof.

The present invention also includes a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds described above and a pharmaceutically acceptable carrier. In one embodiment is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. The present invention further includes a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

The present invention further includes a pharmaceutical composition as described in the preceding paragraph further comprising a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor. In one embodiment, the testosterone 5-alpha reductase inhibitor is a type 1, a type 2, both a type 1 and a type 2 (i.e., a three component combination comprising any of the compounds described above combined with both a type 1 testosterone 5-alpha reductase inhibitor and a type 2 testosterone 5-alpha reductase inhibitor), or a dual type 1 and type 2 testosterone 5-alpha reductase inhibitor. In another embodiment, the testosterone 5-alpha reductase inhibitor is a type 2 testosterone 5-alpha reductase inhibitor. The testosterone 5-alpha reductase inhibitor is suitably finasteride.

The present invention also includes a method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of any of the compounds (or any of the compositions) described above. In one embodiment of the method of treating BPH, the compound (or composition) does not cause a fall in blood pressure at dosages effective to alleviate BPH. In another embodiment of the method of treating BPH, the compound is administered in combination with a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor. A suitable testosterone 5-alpha reductase inhibitor for use in the method is finasteride.

The present invention also includes a method of inhibiting contraction of prostate tissue or relaxing lower urinary tract tissue in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of

any of the compounds (or any of the compositions) described above. In one embodiment of the method of inhibiting contraction of prostate tissue or relaxing lower urinary tract tissue, the compound (or composition) additionally does not cause a fall in blood pressure at dosages effective to inhibit contraction of prostate tissue. In another embodiment, the compound is administered in combination with a testosterone 5-alpha reductase inhibitor; the testosterone 5-alpha reductase inhibitor is suitably finasteride.

The present invention also includes a method of treating a disease which is susceptible to treatment by antagonism of the alpha 1a receptor which comprises administering to a subject in need thereof an amount of any of the compounds described above effective to treat the disease. Diseases which are susceptible to treatment by antagonism of the alpha 1a receptor include, but are not limited to, BPH, high intraocular pressure, high cholesterol, impotency, sympathetically mediated pain, migraine (see Vatz, *Headache* (1997), 37: 107-108) and cardiac arrhythmia.

The present invention also includes a method of preventing or treating prostatic cancer which comprises administering to a subject in need of prevention or treatment thereof a therapeutically effective amount of a combination comprising any of the compounds (or compositions) described above and a testosterone 5-alpha reductase inhibitor. The testosterone 5-alpha reductase inhibitor is suitably finasteride.

The present invention also includes the use of any of the compounds described above in the preparation of a medicament for: a) treating benign prostatic hyperplasia; b) relaxing lower urinary tract tissue; or c) inhibiting contraction of prostate tissue; in a subject in need thereof.

The present invention further includes the use of any of the alpha 1a antagonist compounds described above and a 5-alpha reductase inhibitor for the manufacture of a medicament for: a) treating benign prostatic hyperplasia; b) relaxing lower urinary tract tissue; or c) inhibiting contraction of prostate tissue which comprises an effective amount of the alpha 1a antagonist compound and an effective amount of 5-alpha reductase inhibitor, together or separately.

As used herein, the term "C_1-C_6 alkyl" means linear or branched chain alkyl groups having from 1 to 6 carbon atoms and includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and

methyl. "C_1-C_4 alkyl" means n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "C_1-C_6 alkoxy" means an -O-alkyl group wherein alkyl is C_1 to C_6 alkyl. "C_1-C_4 alkoxy" has an analogous meaning; i.e., it is an alkoxy group selected from methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, and sec-butoxy.

The term "C_2-C_8 alkoxyalkyl" means a linear or branched C_1 - C_6 alkyl group as defined above having as a substituent a C_1-C_6 alkoxy group as defined above, wherein the alkoxyalkyl group has a total of from 2 to 8 carbon atoms. Representative examples of suitable alkoxyalkyl groups include, but are not limited to, the C_1-C_6 alkoxy-substituted methyl groups (methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, and the butyloxymethyl, pentyloxymethyl, and hexyloxymethyl isomers), and the C_1-C_6 alkoxy-substituted ethyl groups. Other suitable alkoxyalkyl groups include the series $(CH_2)_{1-6}OCH_3$, $(CH_2)_{1-4}OCH_3$, $(CH_2)_{1-6}OCH_2CH_3$, and $(CH_2)_{1-4}OCH_2CH_3$.

The term "C_3-C_8 cycloalkyl" means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl). The term "C_3-C_6 cycloalkyl" refers to a cyclic ring selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. "C_4-C_6 cycloalkyl" has an analogous meaning.

The term "halogen" (which may alternatively be referred to as "halo") refers to fluorine, chlorine, bromine and iodine (alternatively, fluoro, chloro, bromo, and iodo).

The term "fluorinated C_1-C_6 alkyl" (which may alternatively be referred to as "C_1-C_6 fluoroalkyl") means a C_1 to C_6 linear or branched alkyl group as defined above with one or more fluorine substituents. The term "fluorinated C_1-C_4 alkyl" has an analogous meaning. Representative examples of suitable fluoroalkyls include the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.), 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 3,3,3-trifluoroisopropyl, 1,1,1,3,3,3-hexafluoroisopropyl, and perfluorohexyl.

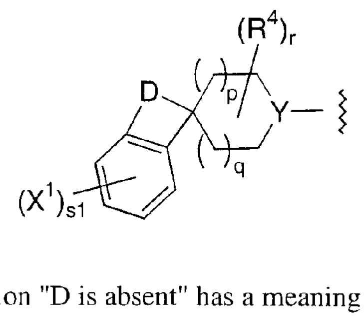
The term "fluorinated C_3-C_8 cycloalkyl" (which may alternatively be referred to as "C_3-C_8 fluorocycloalkyl") means a cycloalkyl group as defined above with one or more fluorine substituents. The terms "fluorinated C_3-C_7 cycloalkyl" and "fluorinated C_3-C_6 cycloalkyl" have analogous meanings. Representative examples

of suitable fluorocycloalkyls include all isomers of fluorocyclohexyl (i.e., 1-, 2-, 3-, and 4-fluorocyclohexyl), difluorocyclohexyl (e.g., 2,4-difluorocyclohexyl, 3,4-difluorocyclohexyl, etc.), fluorocyclopentyl, and so forth.

The term "fluorinated C_1-C_6 alkoxy" (which may alternatively be referred to as "C_1-C_6 fluoroalkoxy") means a C_1-C_6 alkoxy group as defined above wherein the alkyl moiety has one or more fluorine substituents. The term "fluorinated C_1-C_4 alkoxy" has an analogous meaning. Representative examples include the series $O(CH_2)_{0-4}CF_3$ (i.e., trifluoromethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoro-n-propoxy, etc.), 1,1,1,3,3,3-hexafluoroisopropoxy, and so forth.

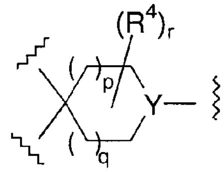
The term "fluorinated C_2-C_8 alkoxyalkyl" means C_2-C_8 alkoxyalkyl as defined above, wherein either or both the alkoxy moiety and the alkyl moiety has one or more fluorine substituents. Representative examples of suitable fluorinated alkoxyalkyl groups include, but are not limited to, the C_1-C_6 fluoroalkoxy-substituted methyl groups (e.g., fluoromethoxymethyl, 2-fluoroethoxymethyl, and 3-fluoro-n-propoxymethyl), C_1-C_6 difluoroalkoxymethyl groups (e.g., difluoromethoxymethyl and 2,2-difluoroethoxymethyl), C_1-C_6 trifluoroalkoxy-substituted methyl groups (e.g., trifluoromethoxymethyl and 2,2,2-trifluoroethoxymethyl), C_1-C_6 alkoxy-substituted fluoromethyl groups (e.g., methoxy- or ethoxy-fluoromethyl), and C_1-C_6 alkoxy-substituted difluoromethyl groups (e.g., methoxy- or ethoxy-difluoromethyl). Other suitable fluorinated alkoxyalkyl groups include the series $(CH_2)_{1-6}OCF_3$, $(CH_2)_{1-4}OCF_3$, $(CH_2)_{1-6}OCH_2CF_3$, and $(CH_2)_{1-4}OCH_2CF_3$.

The expression "E is absent" means that E is replaced by a bond connecting the atoms/moieties to which E would otherwise be attached. Thus, when E is absent, the left-most portion of the compound of Formula (I) may be represented as:

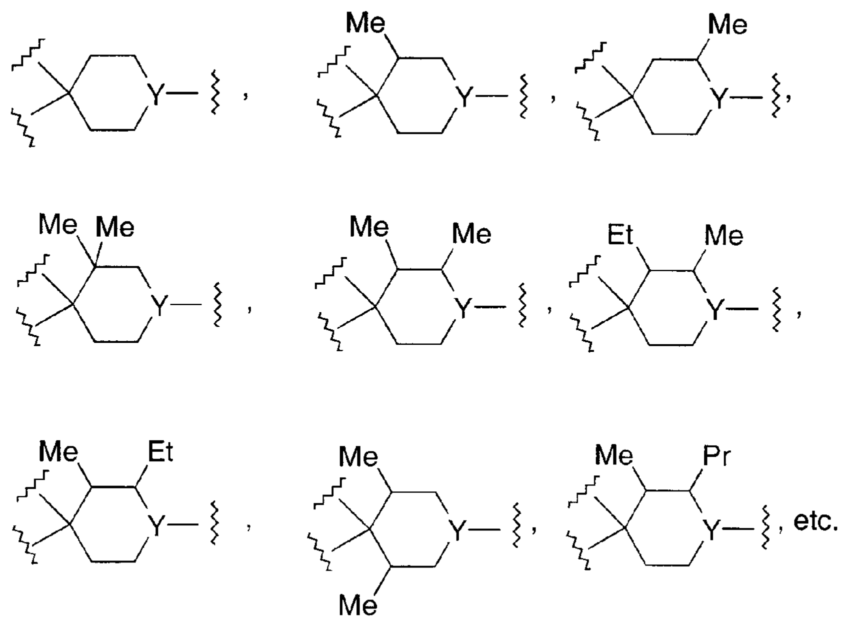


The expression "D is absent" has a meaning analogous to that of "E is absent", as just described.

It is understood that the definition of a substituent (e.g., CO_2R^e) or variable (e.g., R^e) at a particular location in a molecule is independent of its definitions at other locations in that molecule. Thus, for example, when R^1 is $CH_2CO_2R^e = CH_2CO_2H$, and R^7 is $CH_2CO_2R^e$, it is understood that $CH_2CO_2R^e$ in R^7 can be any one of CH_2CO_2H, CH_2CO_2Me, CH_2CO_2Et, CH_2CO_2Pr, etc. As another example, the moiety



wherein R^4 is hydrogen or C_1-C_4 alkyl, p = 1, q =1, and r = 2, represents moieties such as



It is also understood that the definition of a substituent or variable at a particular location in a molecule is independent of the definition of another occurrence of the same substituent or variable at the same location. Thus, $C(=O)N(R^e)_2$ represents groups such as $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)NHC_2H_5$, $-C(=O)N(CH_3)C_2H_5$, etc.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by the methods set forth below and, when viewed in the light of this disclosure, by techniques known in the art. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

Representative embodiments for the variables and substituents set forth in Formula (I) include the following:

R^1 is hydrogen, C_1-C_6 alkyl, or $(CH_2)_{1\text{-}4}CF_3$; or is hydrogen or C_1-C_4 alkyl; or is hydrogen.

Each of R^2 and R^3 is hydrogen or C_1-C_4 alkyl; or is hydrogen, methyl, or ethyl; or is hydrogen. In another embodiment, one of R^2 and R^3 is hydrogen and the other of R^2 and R^3 is hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl. In still another embodiment, one of R^2 and R^3 is hydrogen and the other of R^2 and R^3 is hydrogen or C_1-C_4 alkyl.

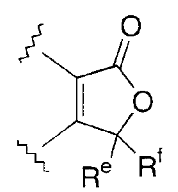
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $C(=O)R^d$, $(CH_2)_{0\text{-}2}CO_2R^e$, $(CH_2)_{0\text{-}2}C(=O)N(R^e)_2$, or SO_2R^d;

R^6 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{1\text{-}3}OR^d$ or $(CH_2)_{0\text{-}3}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:



R^7 is hydrogen, C_1-C_6 alkyl, or $(CH_2)_{1\text{-}4}CF_3$; or is hydrogen or C_1-C_4 alkyl; or is hydrogen.

R^8 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$.

R^9 and R^{10} are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$; or one of R^9 and R^{10} is hydrogen and the other of R^9 and R^{10} is CO_2R^e or $C(=O)N(R^e)_2$.

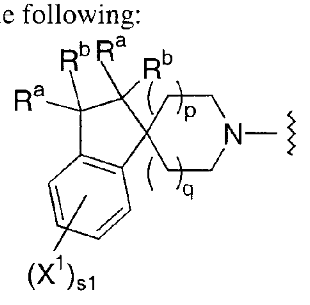
R^{11} is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$.

Each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, fluorinated C_1-C_4 alkyl, fluorinated C_3-C_7 cycloalkyl, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{0\text{-}4}C(=O)N(R^h)_2$, C_1-C_4 alkoxy, fluorinated C_1-C_4 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl; or each is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$; or is independently hydrogen, fluorine, chlorine, cyano, methyl, ethyl, methoxy, ethoxy, CF_3, or OCF_3; or is independently hydrogen, fluorine, chlorine, or methyl; or is independently hydrogen, chlorine, or fluorine.

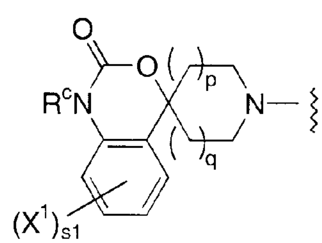
D is absent, $[C(R^aR^b)]_{1\text{-}4}$, $C(R^a)$=$C(R^b)$, $[C(R^aR^b)]_{1\text{-}2}O$, or $O[C(R^aR^b)]_{1\text{-}2}$; or D is absent, $[C(R^aR^b)]_{1\text{-}4}$, or $[C(R^aR^b)]_{1\text{-}2}O$; or D is absent or $(CH_2)_{1\text{-}4}$.

E is absent, C(=O), C(=O)O, $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$, or $N(R^c)C(=O)O$, provided that (i) when E is absent, D is $[C(R^aR^b)]_{2\text{-}4}$, $C(R^a)$=$C(R^b)$, $[C(R^aR^b)]_{1\text{-}2}O$, or $O[C(R^aR^b)]_{1\text{-}2}$; (ii) when E is C(=O) or C(=O)O, D is $C(R^aR^b)$ or $C(R^aR^b)C(R^aR^b)$; and (iii) when E is $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$ or $N(R^c)C(=O)O$, D is absent or $C(R^aR^b)$.

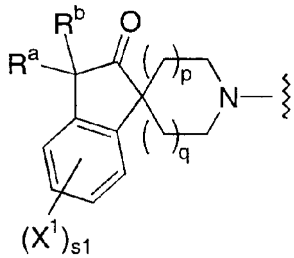
Spirobicyclic groups embodying particular combinations of D and E include the following:



D is $[C(R^aR^b)]_2$;
E is absent

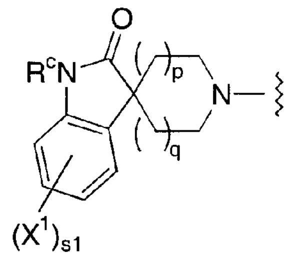


D is absent;
E is $N(R^c)C(=O)O$



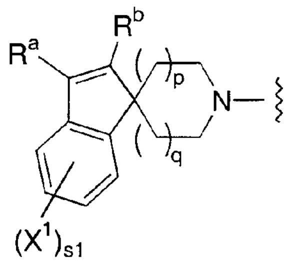
,

D is $C(R^aR^b)$;
E is $C(=O)$



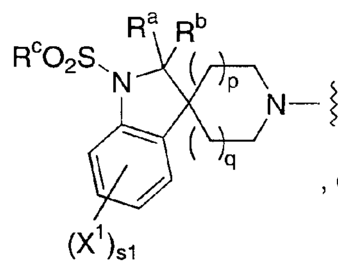
,

D is absent;
E is $N(R^c)C(=O)$



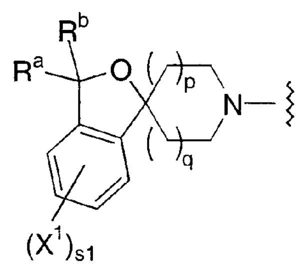
,

D is $C(R^a)=C(R^b)$;
E is absent



, or

D is absent;
E is $N(SO_2R^c)C(R^aR^b)$



D is $C(R^aR^b)O$;
E is absent .

Each of X^2, X^3, and X^4 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_7 cycloalkyl, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{0\text{-}4}C(=O)N(R^h)_2$, C_1-C_4 alkoxy, fluorinated C_1-C_4 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl; or is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3,

$(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$; or is independently hydrogen, chlorine, fluorine, cyano, methyl, ethyl, CF_3, methoxy, ethoxy, OCF_3, CO_2CH_3, $CH_2CO_2CH_3$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$; or is independently hydrogen, fluorine, chlorine, or methyl; or is independently hydrogen or fluorine.

R^a and R^b are each independently hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0-4}CF_3$; or are each independently hydrogen, methyl, or ethyl; or are each independently hydrogen or methyl; or are both hydrogen.

R^c is hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0-4}CF_3$; or is hydrogen, methyl, or ethyl; or is hydrogen.

R^d is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or $(CH_2)_{0-2}CF_3$; or is hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0-2}CF_3$; or is hydrogen, methyl, ethyl, or CF_3; or is hydrogen.

R^e is hydrogen, C_1-C_4 alkyl, C_4-C_6 cycloalkyl, or $(CH_2)_{1-2}CF_3$; or is hydrogen, C_1-C_4 alkyl, or $(CH_2)_{1-2}CF_3$; or is hydrogen, methyl, or ethyl; or is hydrogen.

R^f and R^g are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl; or are each independently hydrogen or C_1-C_4 alkyl; or are each hydrogen.

m is an integer from 2 to 5, or from 2 to 4; or is 2 or 3; or is 3; or is 4.

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2.

Each of s1, s3 and s4 is independently is an integer from zero to 2; or is zero or 1.

s2 is an integer from zero to 3; or is an integer from zero to two; or is zero or 1.

u is an integer from 1 to 2.

v is an integer from 1 to 3; or is an integer from 1 to 2.

In one embodiment, u and v are each integers of from 1 to 2.

The compounds of the present invention typically exhibit selectivity for the human alpha 1a adrenergic receptor. One implication of this selectivity is that these compounds display selectivity for lowering intraurethral pressure without substantially affecting diastolic blood pressure.

Representative compounds of this invention display submicromolar affinity for the human alpha 1a adrenergic receptor subtype while displaying lower

affinity for the human alpha 1d and alpha 1b adrenergic receptor subtypes, and many other G-protein coupled human receptors. A class of the compounds of this invention exhibit nanomolar and subnanomolar affinity for the human alpha 1a adrenergic receptor subtype while displaying at least about 10 fold lower affinity for the human alpha 1d and alpha 1b adrenergic receptor subtypes, and many other G-protein coupled human receptors (e.g., serotonin, dopamine, alpha 2 adrenergic, beta adrenergic or muscarinic receptors). In a subclass of the preceding class, the compounds of this invention exhibit nanomolar and subnanomolar affinity for the human alpha 1a adrenergic receptor subtype while displaying at least about 40-fold lower affinity for the human alpha 1d and alpha 1b adrenergic receptor subtypes, in addition to exhibiting selectivity over other G-protein coupled human receptors (e.g., serotonin, dopamine, alpha 2 adrenergic, beta adrenergic or muscarinic receptors). In another subclass of the preceding class, the compounds of this invention exhibit nanomolar and subnanomolar affinity for the human alpha 1a adrenergic receptor subtype while displaying at least about 100-fold lower affinity for the human alpha 1d and alpha 1b adrenergic receptor subtypes, in addition to exhibiting selectivity over other G-protein coupled human receptors (e.g., serotonin, dopamine, alpha 2 adrenergic, beta adrenergic or muscarinic receptors).

These compounds are administered in dosages effective to antagonize the alpha 1a receptor where such treatment is needed; e.g., treatment of BPH. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or in the prepartion of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include the following:

Acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, n-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate.

Compounds of this invention are used to reduce the acute symptoms of BPH. Thus, compounds of this invention may be used alone or in combination with more long-term anti-BPH therapeutics, such as testosterone 5-a reductase inhibitors, including PROSCAR® (finasteride). Aside from their utility as anti-BPH agents, these compounds may be used to induce highly tissue-specific, localized alpha 1a adrenergic receptor blockade whenever this is desired. Effects of this blockade include reduction of intraocular pressure, control of cardiac arrhythmias, and possibly a host of alpha 1a receptor mediated central nervous system events.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

The present invention further includes metabolites of the compounds of the present invention. Metabolites include active species produced upon introduction of compounds of this invention into the biological milieu.

When compounds according to the invention have at least one chiral center, they may accordingly exist as enantiomers or as mixtures of enantiomers (e.g., racemic mixtures). Where the compounds according to the invention possess two or more chiral centers, they may additionally exist as diastereoisomers. It is to be

understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the present invention may form solvates with water (i.e., hydrates) or common organic solvents. Such solvates are also encompassed within the scope of this invention.

The term "selective alpha 1a adrenergic receptor antagonist," as used herein, refers to an alpha 1a antagonist compound which exhibits selectivity (e.g., at least about ten fold selectivity) for the human alpha 1a adrenergic receptor as compared to the human alpha 1b, alpha 1d, alpha 2a, alpha 2b and alpha 2c adrenergic receptors.

The term "lower urinary tract tissue," as used herein, refers to and includes, but is not limited to, prostatic smooth muscle, the prostatic capsule, the urethra and the bladder neck.

The term "subject," as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated.

The present invention includes pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate

or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

As used herein, the term "composition" encompasses a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Where the processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

The specificity of binding of compounds showing affinity for the alpha 1a receptor is shown by comparing affinity to membranes obtained from transfected cell lines that express the alpha 1a receptor and membranes from cell lines or tissues known to express other types of alpha (e.g., alpha 1d, alpha 1b) or beta adrenergic receptors. Expression of the cloned human alpha 1d, alpha 1b, and alpha 1a receptors and comparison of their binding properties with known selective antagonists provides a rational way for selection of compounds and discovery of new compounds with predictable pharmacological activities. Antagonism by these compounds of the human alpha 1a adrenergic receptor subtype may be functionally demonstrated in anesthetized animals. These compounds may be used to increase urine flow without exhibiting hypotensive effects.

The ability of compounds of the present invention to specifically bind to the alpha 1a receptor makes them useful for the treatment of BPH. The specificity of binding of compounds showing affinity for the alpha 1a receptor is compared against the binding affinities to other types of alpha or beta adrenergic receptors. The human alpha adrenergic receptor of the 1a subtype was recently identified, cloned and expressed as described in PCT International Application Publication Nos. WO94/08040, published 14 April 1994 and WO 94/21660, published 29 September 1994. The cloned human alpha 1a receptor, when expressed in mammalian cell lines, is used to discover ligands that bind to the receptor and alter its function. Expression of the cloned human alpha 1d, alpha 1b, and alpha 1a receptors and comparison of their binding properties with known selective antagonists provides a rational way for selection of compounds and discovery of new compounds with predictable pharmacological activities.

Compounds of this invention exhibiting human alpha 1a adrenergic receptor antagonism may further be defined by counterscreening. This is accomplished according to methods known in the art using other receptors responsible

for mediating diverse biological functions. [See e.g., PCT International Application Publication No. WO94/10989, published 26 May 1994; US 5403847, issued April 4, 1995]. Compounds which are both selective amongst the various human alpha1 adrenergic receptor subtypes and which have low affinity for other receptors, such as the alpha 2 adrenergic receptors, the ß-adrenergic receptors, the muscarinic receptors, the serotonin receptors, the histamine receptors, and others are particularly preferred. The absence of these non-specific activities may be confirmed by using cloned and expressed receptors in an analogous fashion to the method disclosed herein for identifying compounds which have high affinity for the various human alpha1 adrenergic receptors. Furthermore, functional biological tests are used to confirm the effects of identified compounds as alpha 1a adrenergic receptor antagonists.

The present invention also has the objective of providing suitable topical, oral, systemic and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compositions containing compounds of this invention as the active ingredient for use in the specific antagonism of human alpha 1a adrenergic receptors can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration. For example, the compounds can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an alpha 1a antagonistic agent.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include, without limitation, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or

suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin. Other dispersing agents which may be employed include glycerin and the like.

For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropylmethacryl-amidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyl-eneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydro-pyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Compounds of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever specific blockade of the human alpha 1a adrenergic receptor is required.

The daily dosage of the products may be varied over a wide range; e.g., from about 0.01 to about 1000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0 and 100 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. An effective amount of the drug is ordinarily supplied at a dosage level of from about

0.0002 mg/kg to about 20 mg/kg of body weight per day. Preferably, the range is from about 0.001 to about 10 mg/kg of body weight per day, and especially from about 0.001 mg/kg to about 7 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

Compounds of this patent disclosure may be used alone at appropriate dosages defined by routine testing in order to obtain optimal antagonism of the human alpha 1a adrenergic receptor while minimizing any potential toxicity. In addition, co-administration or sequential administration of other agents which alleviate the effects of BPH is desirable. Thus, in one embodiment, this invention is administration of compounds of this invention and a human testosterone 5-a reductase inhibitor. Included with this embodiment are inhibitors of 5-alpha reductase isoenzyme 2. Many such compounds are now well known in the art and include such compounds as PROSCAR®, (also known as finasteride, a 4-Aza-steroid; see US 4377584 and 4760071, for example). In addition to PROSCAR®, which is principally active in prostatic tissue due to its selectivity for human 5-a reductase isozyme 2, combinations of compounds which are specifically active in inhibiting testosterone 5-alpha reductase isozyme 1 and compounds which act as dual inhibitors of both isozymes 1 and 2, are useful in combination with compounds of this invention. Compounds that are active as 5a-reductase inhibitors have been described in WO 93/23420, EP 0572166; WO 93/23050; WO 93/23038; WO 93/23048; WO 93/23041; WO 93/23040; WO 93/23039; WO 93/23376; WO 93/23419, EP 0572165; WO 93/23051.

The dosages of the alpha 1a adrenergic receptor and testosterone 5-alpha reductase inhibitors are adjusted when combined to achieve desired effects. As those skilled in the art will appreciate, dosages of the 5-alpha reductase inhibitor and the alpha 1a adrenergic receptor antagonist may be independently optimized and combined to achieve a synergistic result wherein the pathology is reduced more than it would be if either agent were used alone. In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

Thus, in one embodiment of the present invention, a method of treating BPH is provided which comprises administering to a subject in need of treatment any of the compounds of the present invention in combination with finasteride effective to treat BPH. The dosage of finasteride administered to the subject is from about 0.01 mg per subject per day to about 50 mg per subject per day in combination with an alpha 1a antagonist. In one aspect, the dosage of finasteride in the combination is from about 0.2 mg per subject per day to about 10 mg per subject per day, and, in another aspect, from about 1 to about 7 mg per subject to day (e.g., about 5 mg per subject per day).

For the treatment of benign prostatic hyperplasia, compounds of this invention exhibiting alpha 1a adrenergic receptor blockade can be combined with a therapeutically effective amount of a 5a-reductase 2 inhibitor, such as finasteride, in addition to a 5a-reductase 1 inhibitor, such as 4,7ß-dimethyl-4-aza-5a-cholestan-3-one, in a single oral, systemic, or parenteral pharmaceutical dosage formulation. Alternatively, a combined therapy can be employed wherein the alpha 1a adrenergic receptor antagonist and the 5a-reductase 1 or 2 inhibitor are administered in separate oral, systemic, or parenteral dosage formulations. See, e.g., US 4377584 and US 4760071 which describe dosages and formulations for 5a-reductase inhibitors.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

Boc or BOC = t-butyloxycarbonyl
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DHP = dihydropyrmidinone
DMF = N,N-dimethylformamide
EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et = ethyl
Et_3N = triethylamine
FAB MS = fast atom bombardment mass spectroscopy
Hal = halogen or halide
HOBT = 1-hydroxy benzotriazole hydrate
HPLC = high performance liquid chromatography
LDA = lithium diisoproypl amide
LHMDA = lithium hexamethyldisilyl amide (or lithium hexamethyldisilazide)
mCPBA = meta-chloroperbenzoic acid

m.p. = melting point
MeOH = methanol
O_2N-Ph-OCOCl = p-nitrophenylchloroformate
OXA or Oxa = oxazolidinone
Ph = phenyl
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthetic procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

Many of the compounds of the present invention can be prepared by the coupling of a suitable spirobicyclic-substituted azacycloalkane (e.g., azetidine, pyrrolidine, piperidine, hexahydro-1H-azepine, etc.) or spirobicyclic-substituted N-(aminoalkyl)-azacycloalkane (e.g., ω-(aminoalkyl)piperidine) with a suitable derivative or activated form of Q-H, as described more fully below.

As shown in Scheme 1, the spiro[bicyclic azacycloalkyl] compound **C1** can be coupled with a haloalkylated derivative of Q'-H (Q' = Q other than q3) via N-alkylation to obtain **C2**. The haloalkylated derivative (e.g., an N-haloalkyloxazolidinone) can be formed by alkylating Q'-H with a suitable dihaloalkyl compound (e.g., 1,3-dibromopropane). Alternatively, **C1** can be alkylated with a Boc-protected haloalkylamine to afford **C3**, which can then be acylated with an activated version of Q"-H (Q" = q1, q2, or q4) to obtain **C4**. The activated version of Q"-H (e.g., the p-nitrophenylchloroformate derivative of Q"-H) can be obtained by deprotonating Q"-H with a base such as LDA, LHMDA, NaH, KH, or butyllithium, and then reacting the deprotonated species with phosgene or a phosgene equivalent such as (p-NO_2Ph)OCOCl. As still another alternative, a carboxylated derivative of

Q'''-H (Q''' = q3 - the reverse DHP) can be coupled with C3 via amidation to obtain C5.

Scheme 2 provides a general procedure for preparing spiro[bicyclic cycloalkyl] aminoalkylaminocarbonyl compounds of the invention. Reductive amination of spirobicyclic cycloalkanone C6 with a mono-blocked diamino species provides intermediate C7 which can be alkylated with an alkyl halide on the newly generated secondary amine to obtain C8. Deprotection of the terminal blocked amine and acylation using procedures analogous to those set forth in Scheme 1 above provide the desired compounds C9 to C12.

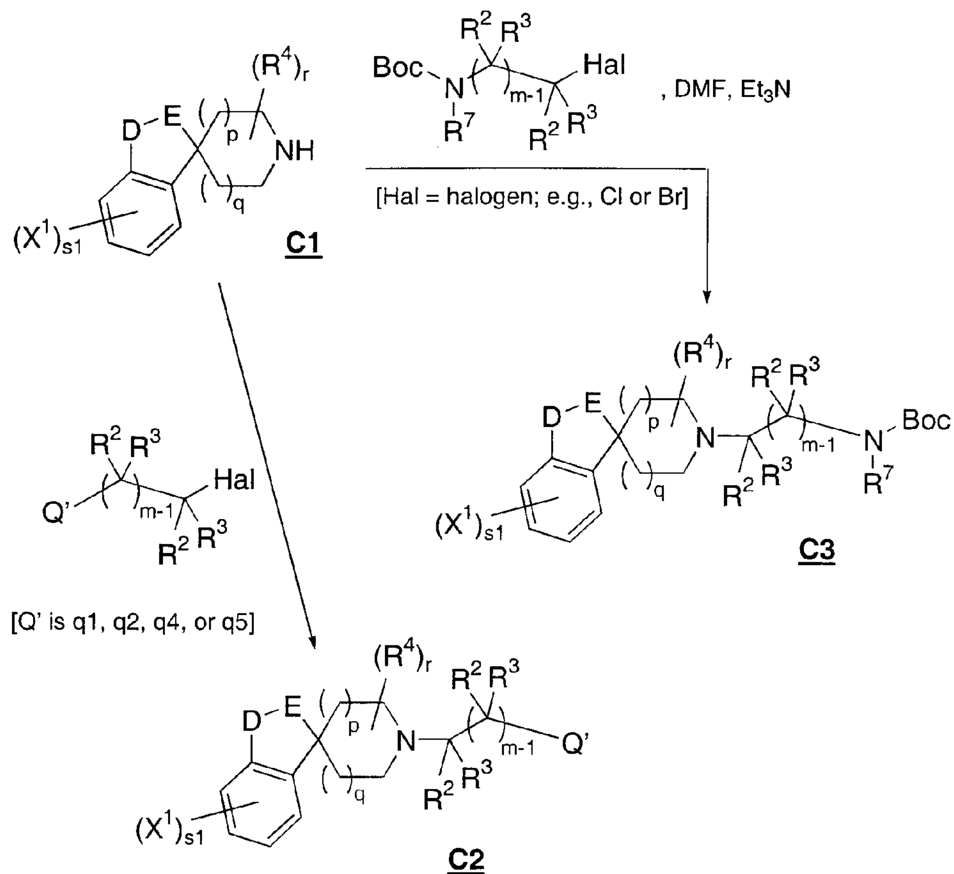
Scheme 3 provides a general procedure for preparing spiro[bicyclic cycloalkyl] aminoalkyl compounds of the invention. Reductive amination of spirobicyclic cycloalkanone C6 with ammonia provides intermediate C13, which can be alkylated with a haloalkylated derivative of Q'-H in analogy with the procedure in Scheme 1 to provide C14.

Scheme 4 provides a general procedure for preparing spiro[bicyclic azacycloalkyl] cycloalkylaminocarbonyl compounds of the invention. Reductive amination of a nitrogen-protected aminocycloalkanone with spirobicyclic azacycloalkyl compound C1 provides the mono-blocked intermediate C15, which can be deprotected and then acylated with activated forms of Q''-H and Q'''-H using procedures analogous to those set forth in Scheme 1 above to afford C16 and C17. Further description of the preparation of aminocycloalkanones and cycloalkylamines and the coupling of the amines to DHP and OXA compounds can be found in WO 99/25345.

Scheme 5 provides a general procedure for preparing spiro[bicyclic azacycloalkyl] cycloalkyl compounds of the invention, wherein reductive amination of a Q''-substituted cycloalkanone with C1 provides C18. This scheme is illustrated in Example 39 below.

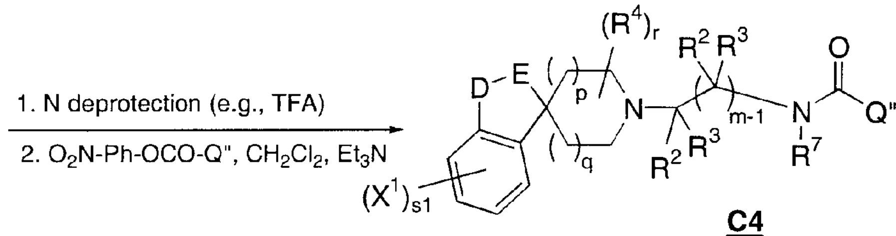
Scheme 6 provides a general procedure for preparing spiro[bicyclic azacycloalkyl] azacycloalkylcarbonyl compounds of the invention. Reductive amination of an N-Boc azacycloalkanone with C1 provides intermediate C19, which can be deblocked and then acylated using procedures analogous to those set forth in Scheme 1 to afford C20 and C21. This scheme is illustrated in Example 38 below.

SCHEME 1



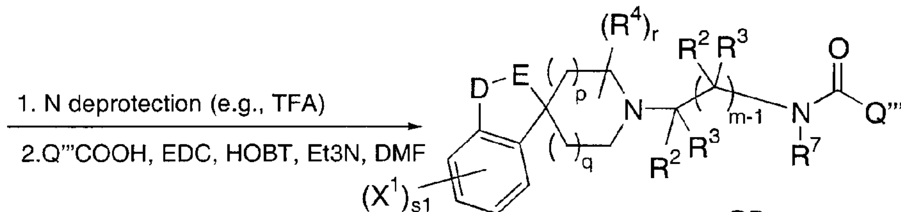
SCHEME 1 (continued)

C3

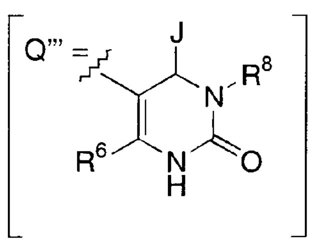


C4

C3

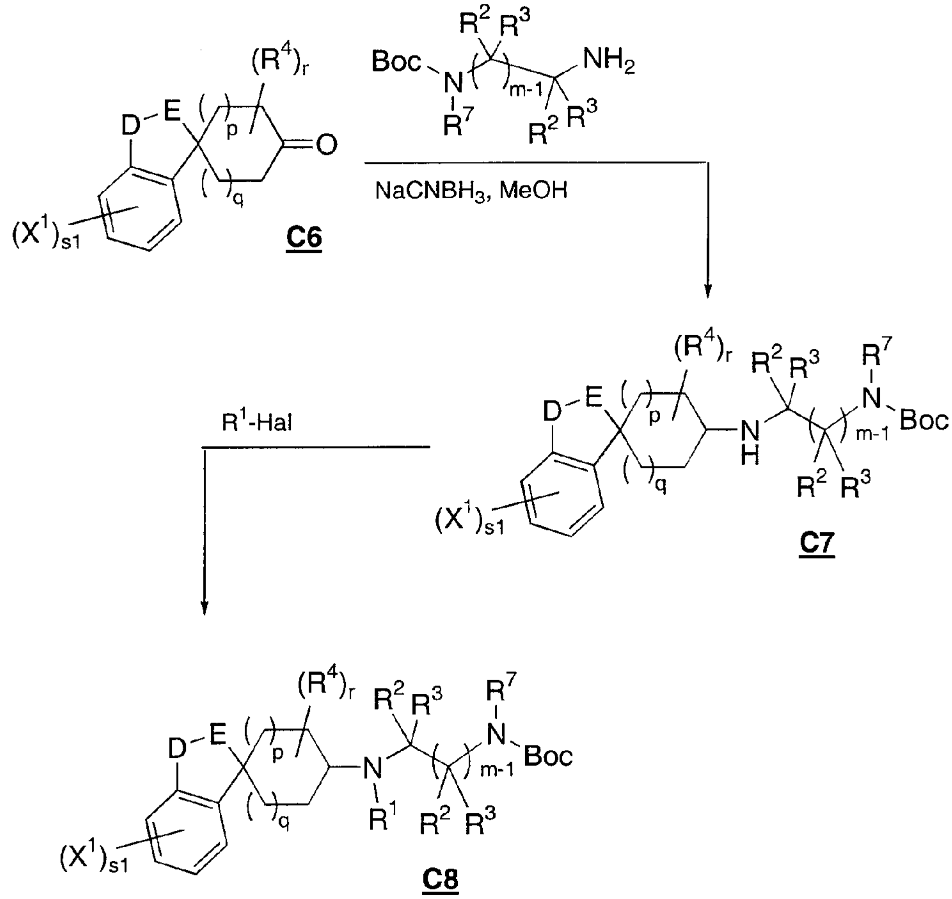


C5

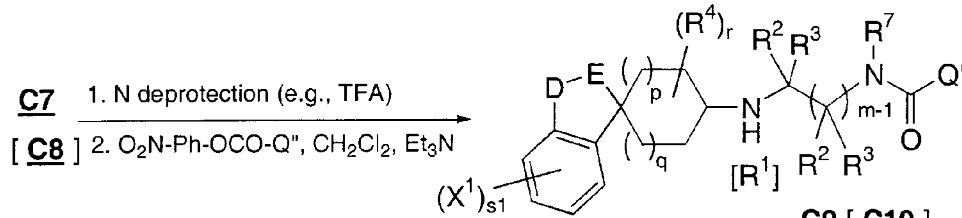


[Q" = q1, q2, or q4]

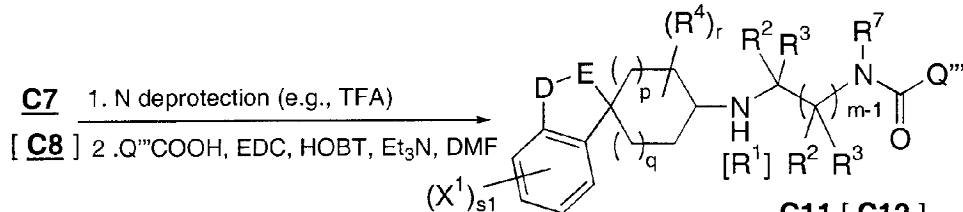
SCHEME 2


(R4)r
D-E
p
q
(X1)s1
O
C6
Boc
N
R7
R2 R3
m-1
NH2
NaCNBH3, MeOH
H
C7
R1-Hal
R1
Boc
C8

SCHEME 2 (continued)



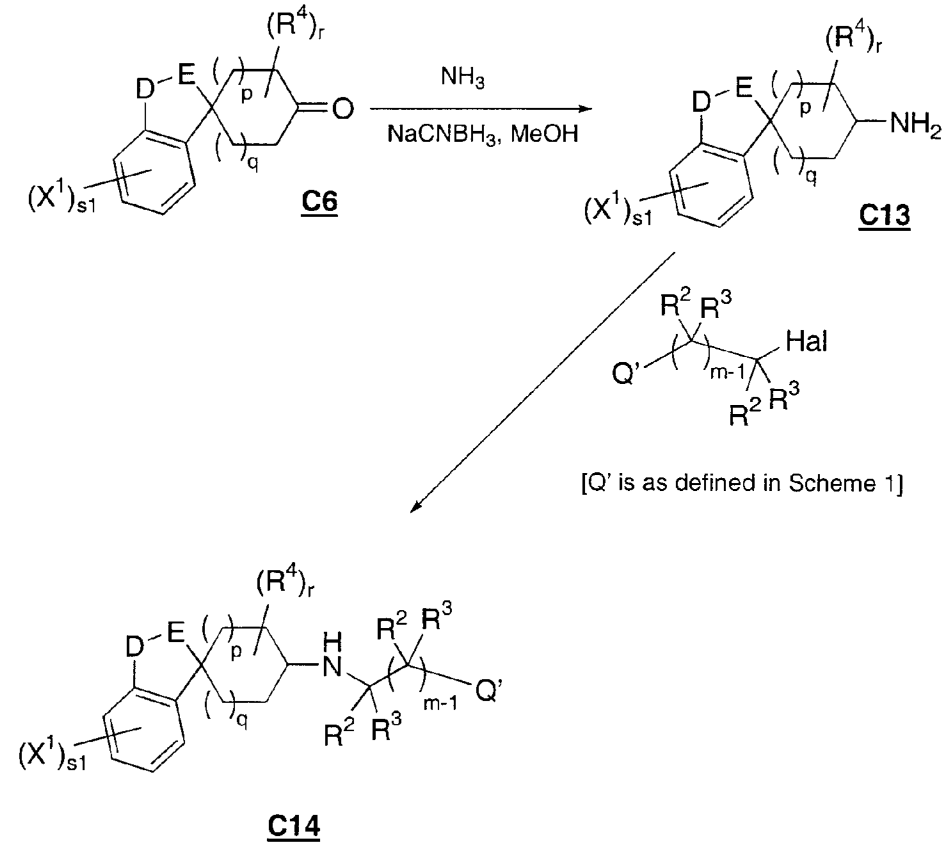
C9 [**C10**]



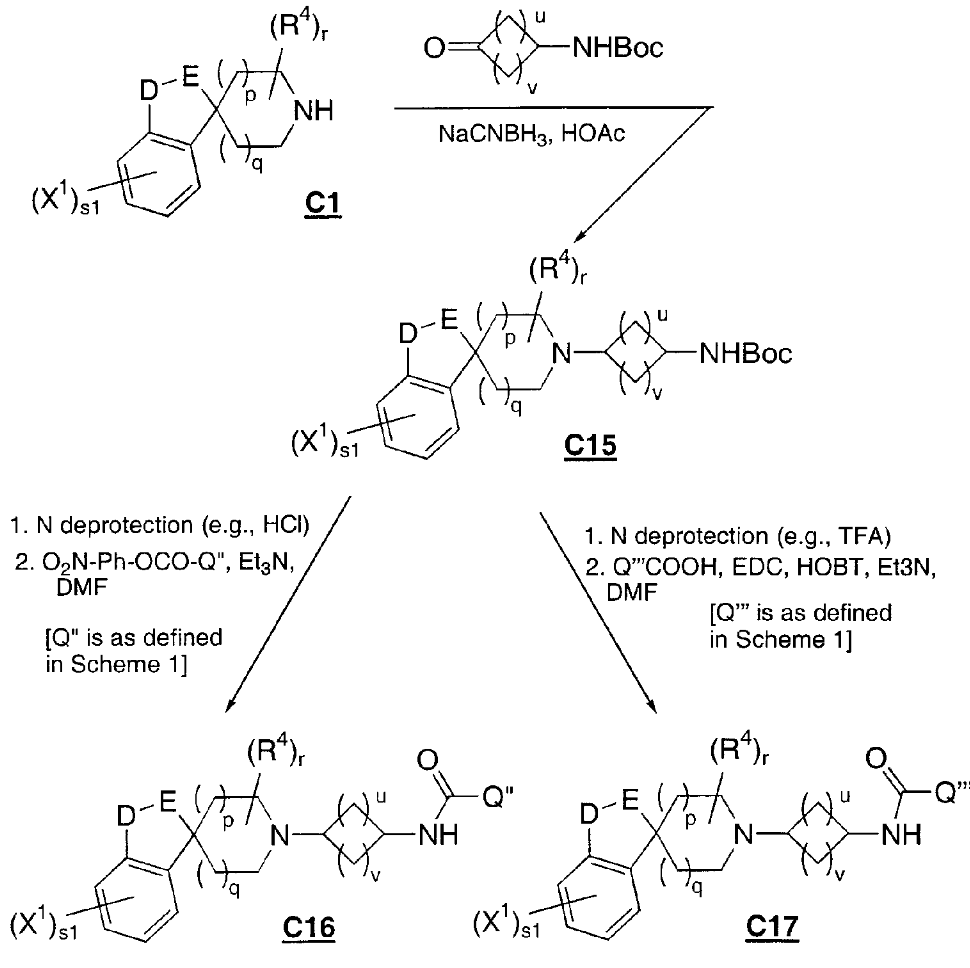
C11 [**C12**]

[Q" and Q''' are each as defined in Scheme 1]

SCHEME 3

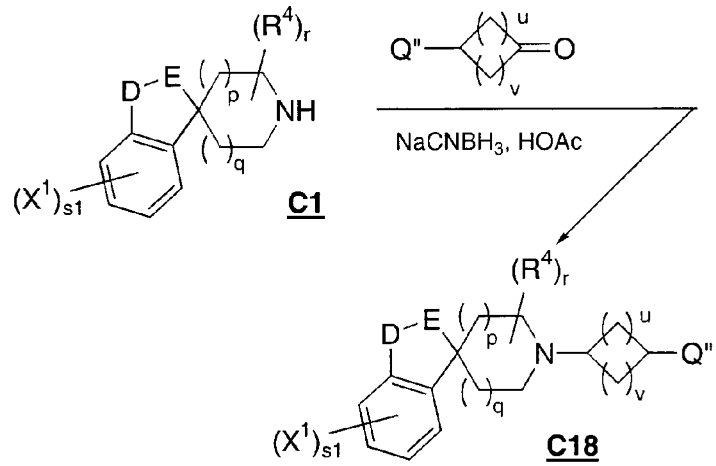


SCHEME 4



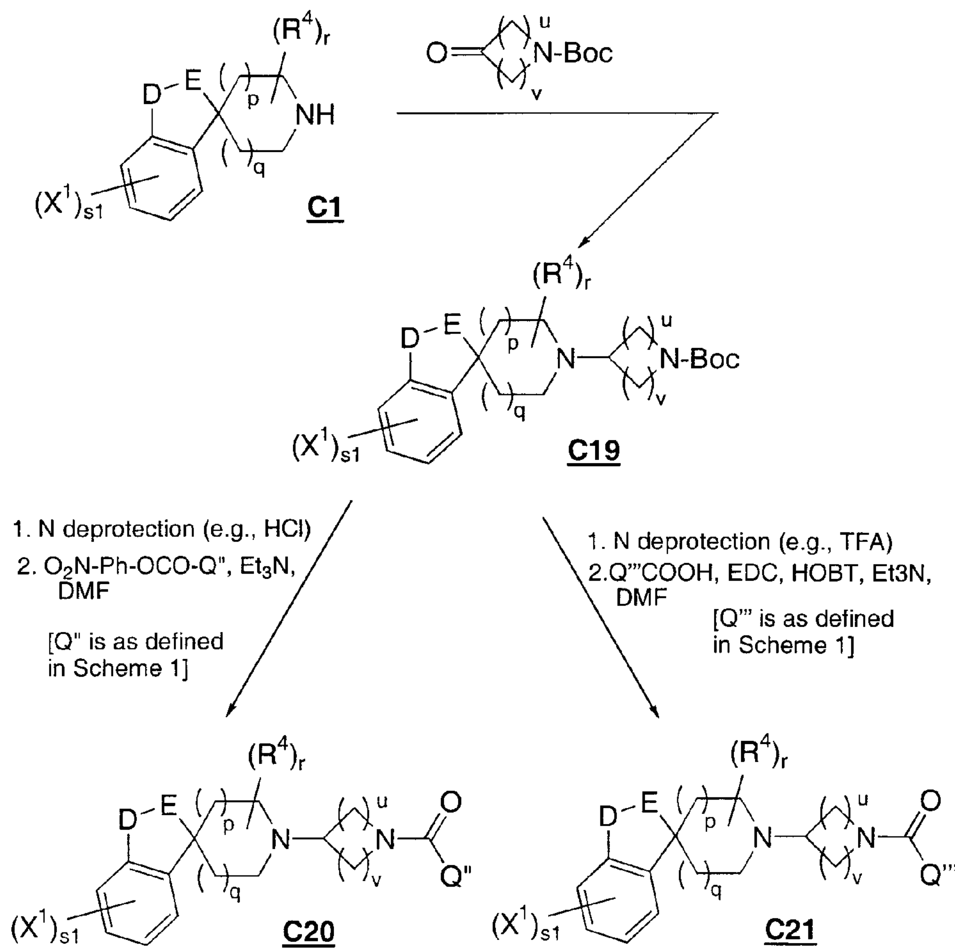
(R4)r
D
E
p
NH
q
(X1)s1
C1
O
u
v
NHBoc
NaCNBH3, HOAc
N
C15
1. N deprotection (e.g., HCl)
2. O2N-Ph-OCO-Q", Et3N, DMF
[Q" is as defined in Scheme 1]
1. N deprotection (e.g., TFA)
2. Q'"COOH, EDC, HOBT, Et3N, DMF
[Q'" is as defined in Scheme 1]
Q"
NH
C16
Q'"
C17

SCHEME 5



[Q" is as defined in Scheme 1]

SCHEME 6



Q'-H, Q"-H, and Q'''-H and derivatives thereof suitable for use in preparing compounds of the invention can be prepared by procedures known to those of ordinary skill in the art. For example, unsubstituted, alkyl- and cycloalkyl-substituted oxazolidinones are prepared and activated in general by published and well developed chemistry, in particular, of Evans. See, e.g., Evans et al., "Stereoselective Aldol Condensations" in *Topics in Stereochemistry* 1982, 13: 1-115. The starting materials, in general, are natural and unnatural amino acids. For instance, some of the compounds are prepared from substituted phenyl glycine derivatives, which after reduction of the carboxylate and a phosgene equivalent mediated cyclization provides the substituted oxazolidinone ring system. Deprotonation with a

strong base such as n-butyl lithium and addition to a phosgene or phosgene equivalent such as a THF solution of p-nitrophenylchloroformate produces the stable, isolable "activated" oxazolidinone.

Oxazolidinones substituted with carboxylate, carboxamide, and alkoxyalkyl can be prepared by hydroxyamination of olefins to provide protected aminoalcohols, using procedures as described in G. Li et al., *Angew. Chem. Int. Ed. Engl.* 1996, 35: 2813-2817. Deprotection under standard conditions followed by a phosgene equivalent to mediate cyclization provides the substituted oxazolidinone ring system. Deprotonation with a strong base, for example, lithium bis(trimethylsilyl)amide, and addition to a THF solution of p-nitrophenylchloroformate (or other phosgene equivalent) produces the stable, isolable "activated" oxazolidinone.

Further description of oxazolidinones, their preparation, and methods for coupling them to amines can be found in WO 98/57940.

Dihydropyrimidinones can be prepared by the condensation reaction of an aldehyde, urea and a 1,3-acetoacetate type derivative catalyzed by a Lewis Acid, a copper (I) species and acetic acid. Activation can be accomplished by treatment with a strong base, for instance, $LiN(TMS)_2$, followed by addition to a THF solution of p-nitrophenylchloroformate. Further description of dihydropyrimidinones, their preparation, and methods for coupling them to amines can be found in WO 96/14846.

Saccharins can be prepared according to known methods; e.g., page 40 and Examples 21 and 22 of WO 96/25934. WO '934 also describes methods for alkylating saccharins and coupling the alkylated saccharins to amines.

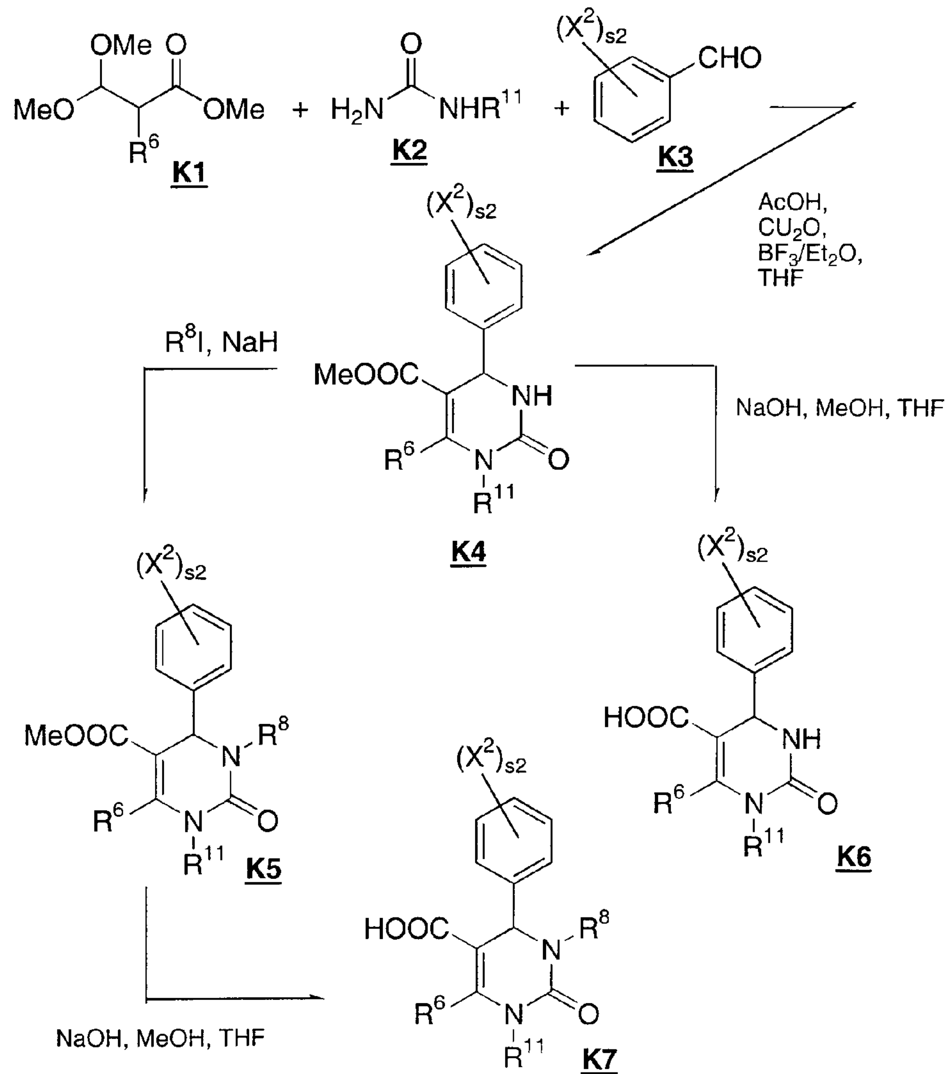
The dihydropyrimidinones and oxazolidinones can be synthesized independently in racemic form, separated utilizing preparative chiral HPLC or other conventional procedures for separating optical isomers (e.g., resolution of diastereomeric salts), and then activated and reacted with the suitable spirobicyclic azacycles and carbocycles.

A general procedure for preparing reverse DHP intermediates (i.e., intermediates of formula Q'''-H) is set forth in Scheme 7, wherein the methylproprionate **K1** is condensed with urea **K2** and arylaldehyde **K3**, catalyzed by acetic acid, copper oxide and a Lewis acid (e.g., $BF_3 \cdot Et_2O$) to obtain the 4-aryl-1,2,3,4-tetrahydropyrimidin-2-one-5-carboxylic acid methyl ester **K4**, which is subsequently converted to the 5-carboxylic acid derivative **K6** by basic hydrolysis. Alternatively, the methyl ester can first be treated with an alkyl or cycloalkyl halide (e.g., an iodide such as methyl iodide) to obtain the 3-alkyl or 3-cycloalkyl derivative

K5, which is then hydrolyzed to the 5-carboxylic acid derivative **K7**. Further description of reverse dihydropyrimidinones, their preparation, and methods for coupling them to amines through various linking groups can be found in WO 96/14846.

Reverse DHP optical isomers can be resolved by using preparative chiral HPLC. They can also be resolved by reacting a mixture of methyl ester enantiomers with LDA and p-nitrophenyl-chloroformate, followed by treatment with R-(+) alpha methyl benzylamine to obtain the 3-(1-phenylethyl-carbamoyl) diastereomers, which are separated by conventional means known in the art. The enantiomers are then obtained from the separated diastereomers first by reaction with DBU to regenerate the methyl ester (e.g., enantiomer of **K4**), followed directly by basic hydrolysis to obtain the corresponding carboxylic acid enantiomer (e.g., enantiomer of **K6**), or followed by reaction with an alkyl or cycloalkyl halide (to provide, e.g., an enantiomer of **K5**) and then hydrolysis to obtain the corresponding carboxylic acid enantiomer (e.g., enantiomer of **K7**).

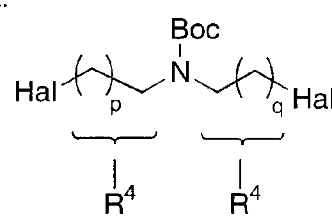
SCHEME 7



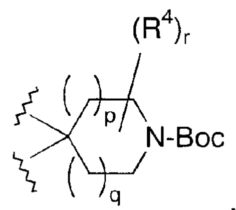
The following references describe preparations of oxazolidinones, dihydropyrimidinones, thiazolidinones, and/or saccharins, and describe the coupling of the oxazolidinones, etc. to various amines: WO 98/57632, WO 9857638, WO 98/57639, WO 98/57640, WO 98/57641, and WO 98/57642. The person of ordinary skill in the art, having knowledge of the instant application, can adapt the teachings of these references to the preparation of compounds of the present invention without undue experimentation.

Many of the spirobicyclic-substituted azacycloalkane compounds employed in the preparation of compounds of the present invention can be made by the methods set forth in Schemes 8 - 13 below. Scheme 8 shows the preparation of spiroindanyl- and spiroindenyl-piperidines, wherein indene **L1** is reacted with a strong base (e.g., LHMDA, LDA, or sodium or potassium hydride) and then with N-Boc-bis-(2-chloroethyl)amine to form the Boc-protected spiroindene piperidine **L2**, which is treated with acid (e.g., TFA in CH_2Cl_2 or HCl in cold EtOAc) to obtain spiro[1H-indeno-1,4'-piperidine] **L3**. Reduction of **L2** (H_2 and palladium on carbon catalyst) followed by nitrogen deprotection (or, alternatively, reduction of **L3**) affords the spiro[indano-1,4'-piperidine] **L4**. For further description of this chemistry, see *J. Med. Chem.* 1992, 35: 2033-2039 and 3919-3927.

Other N-Boc-bis-(haloalkyl)amines can be used in place of N-Boc-bis(2-chloroethyl)amine to provide a wide range of spiroindene and spiroindane azacycloalkanes suitable for preparing compounds of the invention; i.e., Boc-protected amines of formula:



can be used to obtain spirocyclic amines of formula:



Scheme 9 provides a method for forming spiro[indano-1,4'-piperidin]-2-ones, wherein Boc-protected spiroindene piperidine **L5** is treated with a peroxy acid to obtain epoxide intermediate **L6**, which forms the corresponding spiroindan-2-one **L7** upon treatment with a Lewis acid. Nitrogen deprotection by treatment with an acid such as TFA provides **L8**. Alternatively, **L7** can be alkylated on the indanone ring by reaction with alkyl halide and then nitrogen deprotected to afford **L9**.

Scheme 10 shows a method for forming spiro[benzocycloalkane-2,4'-piperidin]-1-ones via chemistry previously described in Scheme 8. Further description of this chemistry can be found in *Biorg. Med. Chem. Lett.* 1998, 8: 107-112. As noted above in discussing Scheme 8, other N-Boc-bis-(haloalkyl)amines can be used in place of N-Boc-bis(2-chloroethyl)amine in this scheme to provide a wide range of spiroindan-1-one azacycloalkanes suitable for preparing compounds of the invention.

Scheme 11 shows a method for forming spiro[isobenzofuran-1(3H),4'-piperidines] and spiro[isobenzofuran-1(3H),4'-piperidin]-3-ones. N-phenylbenzamide **L13** is lithiated with n-butyllithium and then reacted with N-Boc-piperidone to afford N-Boc-spiro[isobenzofuran-1(3H),4'-piperidin]-3-one **L14**, which can be treated with acid to form the deprotected analog **L15**. Alternatively, **L14** can be reduced with borane and then deprotected to provide spiro[isobenzofuran-1(3H),4'-piperidine] **L16**. Further description of this chemistry can be found in *J. Org. Chem.* 1975, 40: 1427-1433.

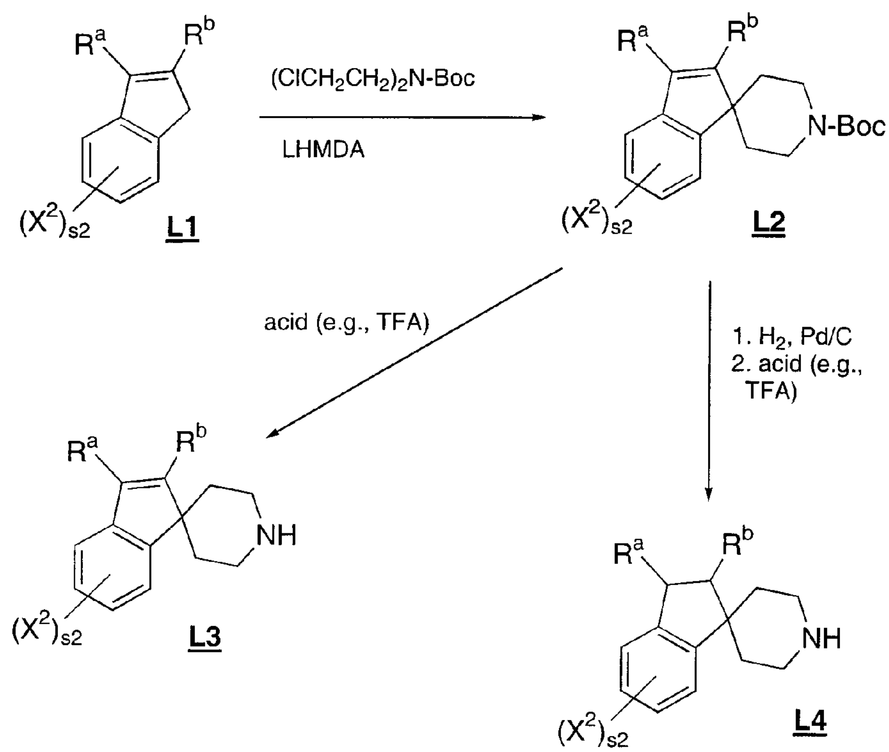
Scheme 12 shows a method for forming spiro[3H-indole-3,4'-piperidin]-2(1H)-ones, in which 3H-indol-2(1H)-one **L17** is treated with a strong base (e.g., LHMDA, LDA, or sodium or potassium hydride) and then with N-Boc-bis-(2-chloroethyl)amine to form the Boc-protected spiroindolyl piperidine **L18**, which is treated with acid (e.g., TFA in CH_2Cl_2 or HCl in cold EtOAc) to obtain **L19**. Further description of this chemistry can be found in *Org. Prep. Proced. Int.* 1995, 27: 691-694. [Note: This reference teaches that the first step of Scheme 12 works with a benzyl-protected reagent, but not with a Boc-protected reagent. Boc-protected reagents have been found herein to work satisfactorily with a suitable choice of strong base.] As noted above in discussing Schemes 8 and 10, other N-Boc-bis-(haloalkyl)amines can be used in place of N-Boc-bis(2-chloroethyl)amine in this scheme to provide a variety of analogs of **L19**.

Scheme 13 shows a method for forming spiro[4H-3,1-benzoxazine-4,4'-piperidine]-2(1H)-ones. Halo-substituted aniline **L20** is treated with di-t-butylcarbonate to obtain **L21**, which is lithiated with t-butyllithium and reacted with a Boc'ed piperidone to obtain Boc-protected halobenzoxazinone **L22**, which can be deprotected by treatment with an acid to form **L24**, or can be N-alkylated on the benzoxazine ring by treatment with an alkyl halide and then deprotected to form **L25**. Alternatively, **L22** can be dehalogneated by treatment with H_2/Pd to obtain **L23**, which can then be nitrogen-deprotected to afford **L26**, or can be N-alkylated and

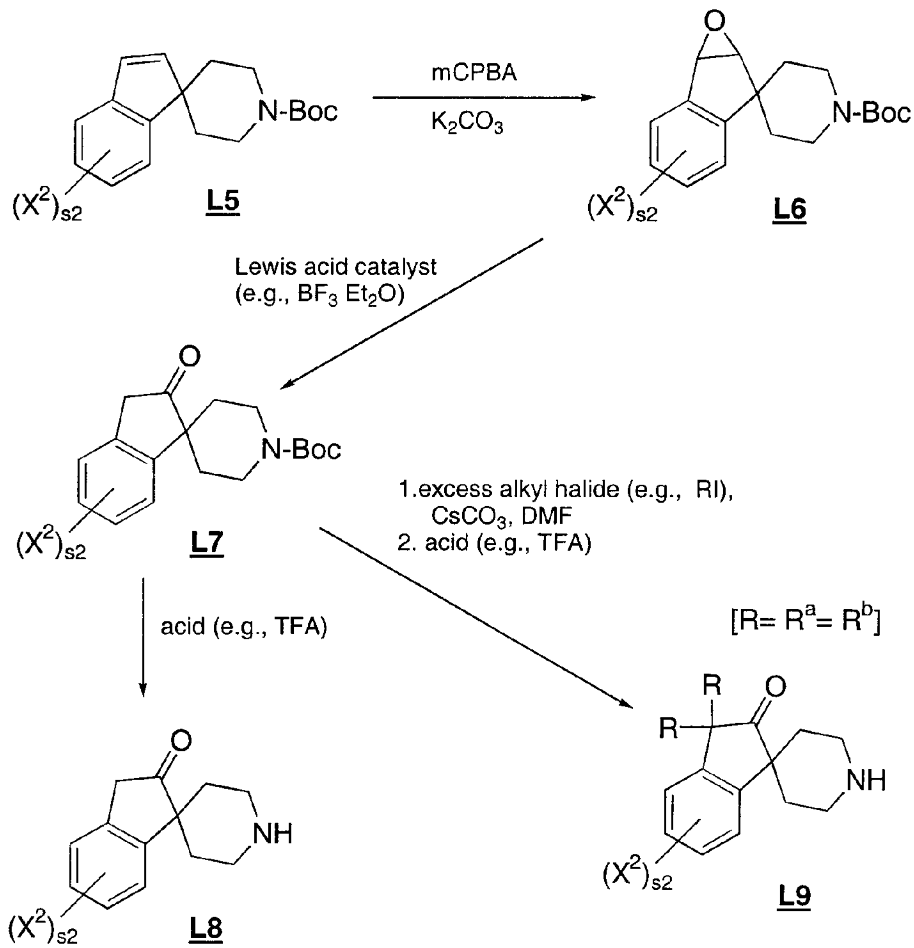
deprotected to form **L27**. Further description of this chemistry can be found in *J. Med. Chem.* 1983, 26: 657-661, *Chem. Pharm. Bull.* 1985, 33: 1129-1139, and US 4349549.

Methods for preparing a variety of 1,2-dihydro-spiro[3H-indole-3,4'-piperidines] are disclosed in US 5536716. For example, the preparations of 1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidine] and spiro[3H-indole-3,4'-piperidine] are respectively described in Example 18, Step A and in Example 21, Step A of US '716.

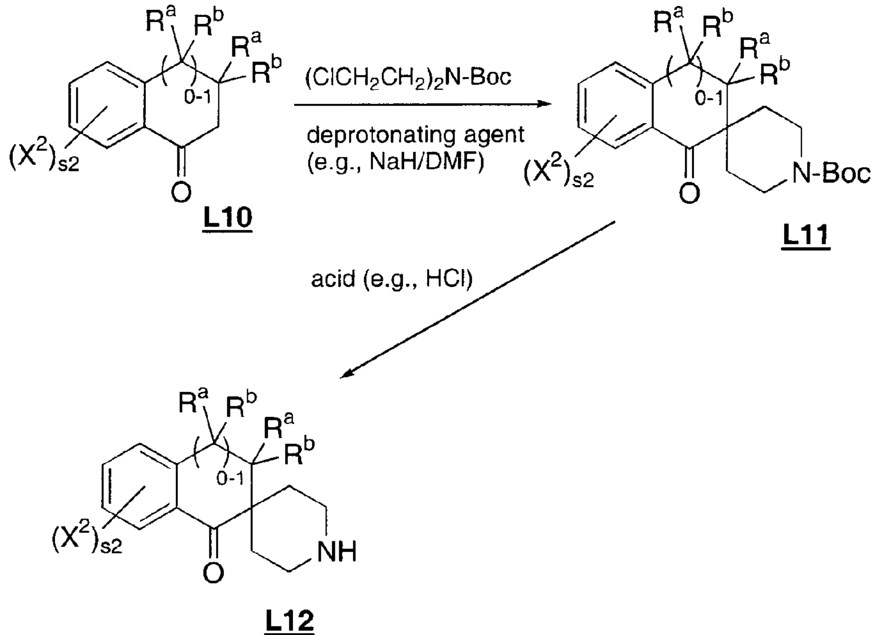
SCHEME 8



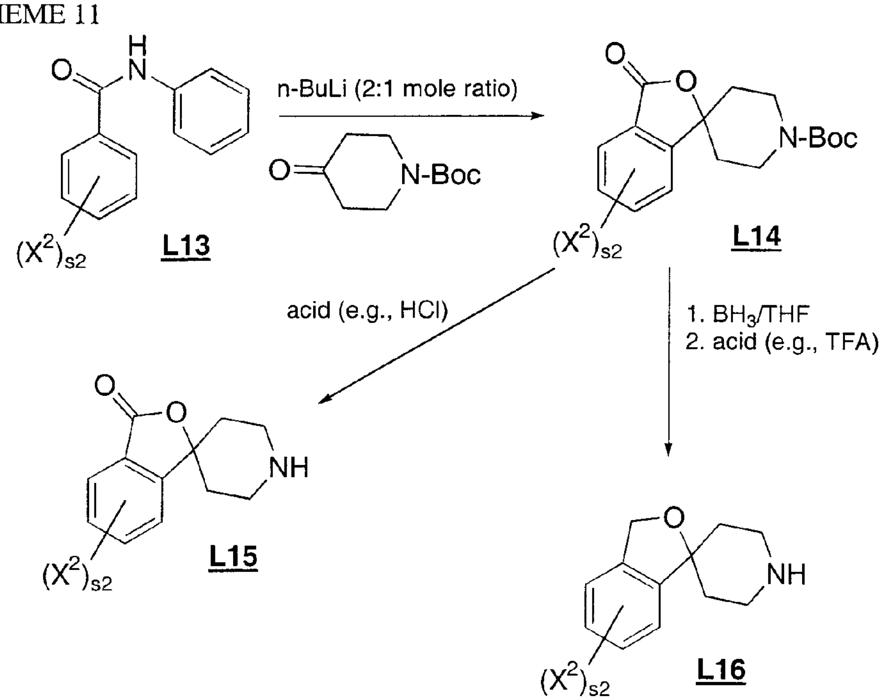
SCHEME 9


mCPBA
K2CO3
N-Boc
(X2)s2
L5
L6
Lewis acid catalyst
(e.g., BF3 Et2O)
L7
1.excess alkyl halide (e.g., RI),
CsCO3, DMF
2. acid (e.g., TFA)
acid (e.g., TFA)
[R= Ra= Rb]
NH
L8
L9

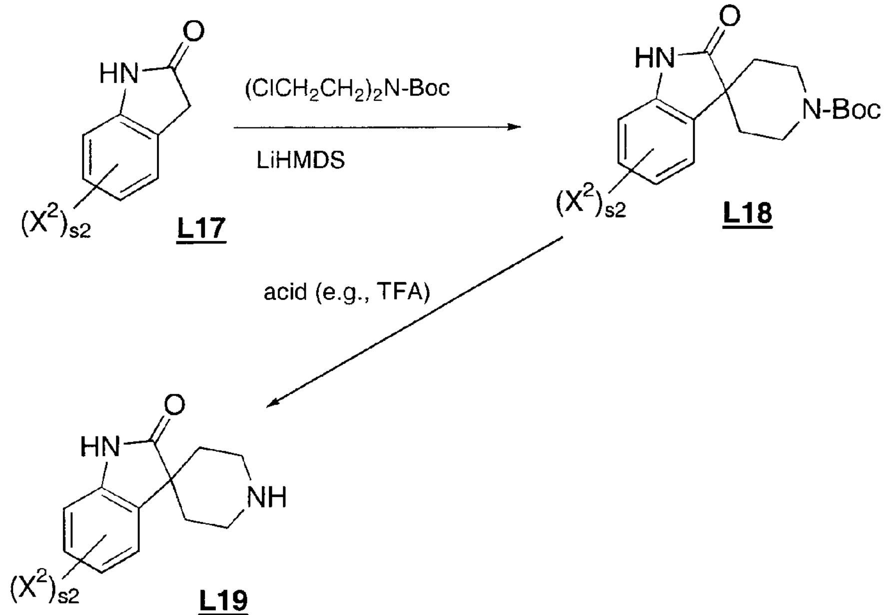
SCHEME 10



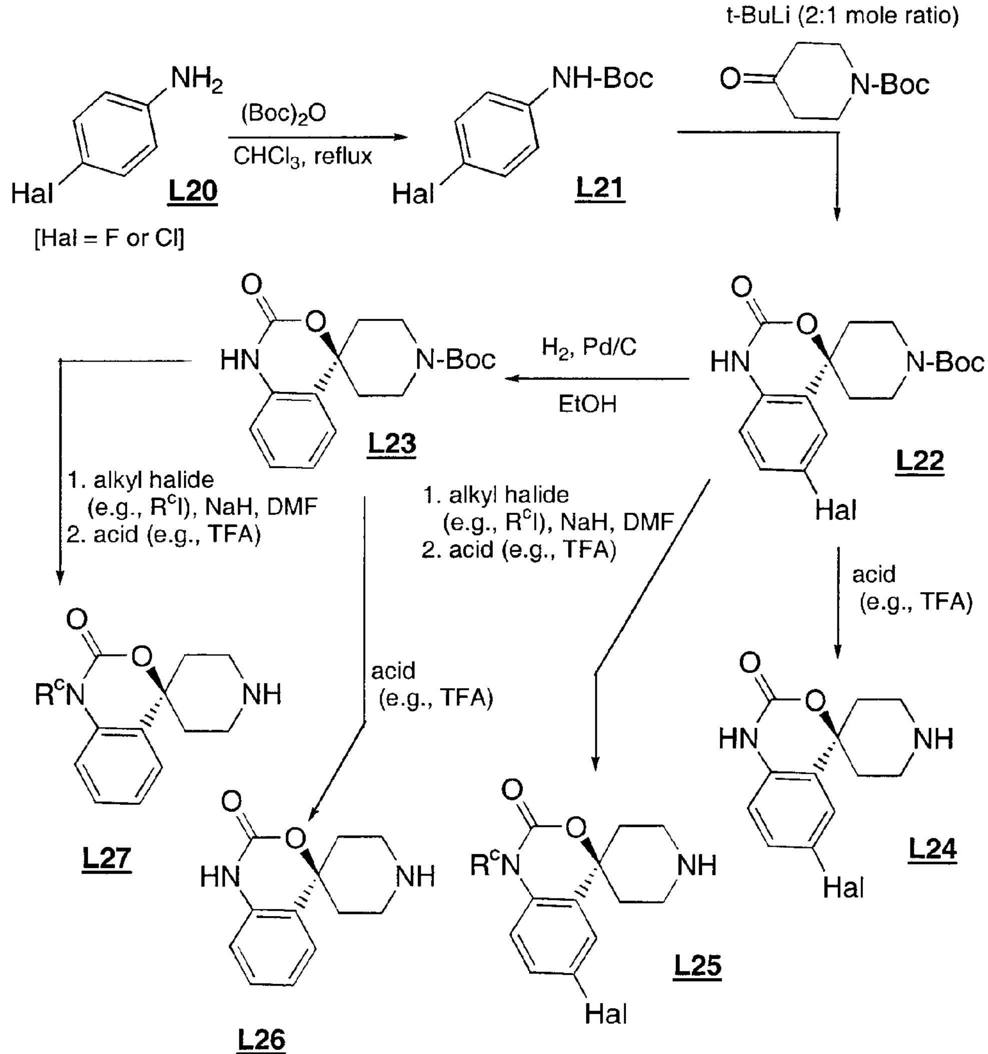
SCHEME 11



SCHEME 12


HN
O
$(ClCH_2CH_2)_2N$-Boc
LiHMDS
$(X^2)_{s2}$
L17
N-Boc
L18
acid (e.g., TFA)
NH
L19

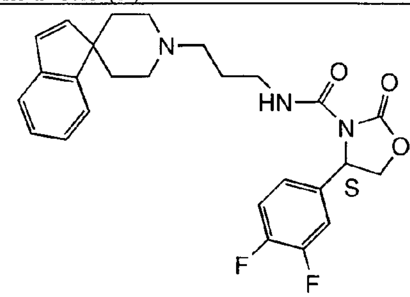
SCHEME 13



The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

3-{[3-(Spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one (**1**)



Step 1: 1'-(3-t-Butoxycarbonylaminopropyl)-spiro[1H-indeno-1,4'-piperidine]

A solution of spiro[1H-indeno-1,4'-piperidine] (382 mg, 2.06 mmol), which was prepared as described in *J. Med. Chem.* 1992, 35, 2033-2039 , and N-t-butoxycarbonyl-3-bromopropylamine (480 mg, 2.07 mmol) in anhydrous dimethyl-formamide (4 mL) containing triethylamine (0.35 mL, 2.5 mmol) was warmed at 50°C for three hours. The reaction mixture was cooled to room temperature, diluted with water and the product was extracted into ethyl acetate. This extract was dried and filtered, and the solvent evaporated to give the title compound as an oil which was used as is.

Step 2: 1'-(3-Aminopropyl)-spiro[1H-indeno-1,4'-piperidine]

The product from step 1 was dissolved in ethyl acetate saturated with HCl gas (7 mL) and stirred at room temperature for 15 hours. The precipitated salt was collected by filtration and a portion (204 mg) was treated with aqueous sat'd sodium carbonate. The freebase was extracted into chloroform. This extract was dried (anhydrous sodium sulfate), filtered through a plug of charcoal and evaporated to give the title compound as an oil.

Step 3: 1-{[3-(Spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine Hydrochloride

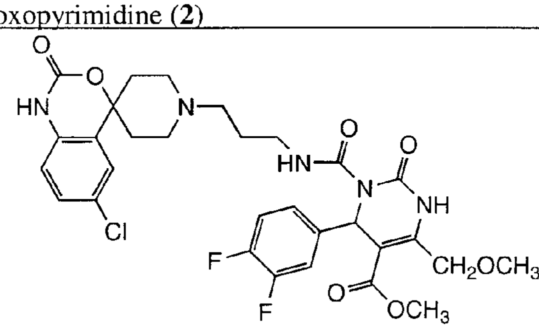
(+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one (72 mg, 0.197 mmol) was added to a solution of 1'-(3-aminopropyl)spiro[1H-indeno-1,4'-piperidine], (48 mg, 0.198 mmol) in methylene

chloride (5 mL) and stirred at r.t. for fifteen hours. The solvent was removed under vacuum and the residue was chromatographed on silica gel eluting with a 0.5 - 2% methanol/ethyl acetate solvent gradient. The purified freebase was isolated as an amorphous solid.

Analysis calc'd for C26H27F2N3O3:
C,66.80; H,5.82; N, 8.99
Found: C,66.53; H,6.11; N, 8.84

EXAMPLE 2

(+/-)-1-{[3-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (**2**)

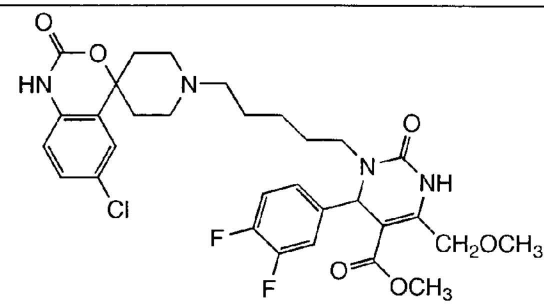


The title compound was prepared according to the procedure described in Example 1 except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] in Step 1 and racemic 5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was used in Step 3 instead of (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one. The freebase was obtained as an amorphous solid.

Analysis calc'd for C30H32ClF2N5O7:
C,55.60; H,4.98; N, 10.81
Found: C,55.53; H,5.08; N, 10.53

EXAMPLE 3

(+/-)-1-{5-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (**3**)



The title compound was prepared according to the procedure described in Example 1, step 1, except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] and racemic 5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-1-(5-bromopentyl)-pyrimidine was substituted for N-t-butoxycarbonyl-3-bromopropylamine. The freebase was obtained as an amorphous solid.

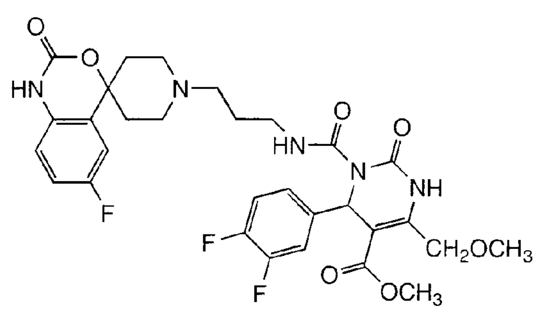
Analysis calc'd for C31H35ClF2N4O6:

C,58.81; H,5.57; N, 8.85

Found: ,58.72; H,5.74; N, 8.64

EXAMPLE 4

(+/-)-1-{[3-(6-Fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (4)



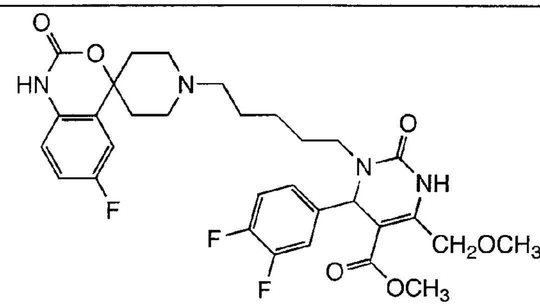
The title compound was prepared according to the procedure described in Example 2 except 6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for 6-chloro-spiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one. The freebase was obtained as an amorphous solid.

Analysis calc'd for C30H32lF3N5O7•0.1 H2O•0.35 C4H10O(ether)

	C,57.19; H,5.45; N, 10.62
Found:	C,57.19; H,5.30; N, 10.54

EXAMPLE 5

(+/-)-1-{5-(6-Fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (5)



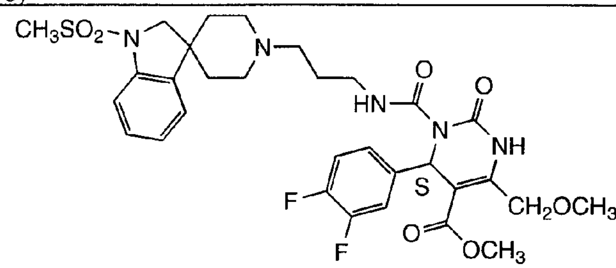
The title compound was prepared according to the procedure described in Example 3 except 6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for 6-chloro-spiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one. The freebase was obtained as an amorphous solid.

Analysis calc'd for C31H35F3N4O6•0.15 H2O•0.45 C4H10O(ether)

	C,60.35; H,6.15; N, 8.58
Found:	C,60.37; H,6.02; N, 8.55

EXAMPLE 6

1-{[3-(1,2-Dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine (**6**)



The title compound was prepared according to the procedure described in Example 1 except 1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidine], which is prepared as described in US 5536716 , was substituted for spiro[1H-indeno-1,4'-piperidine] in step 1, and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in step 3. The freebase was obtained as an amorphous solid.

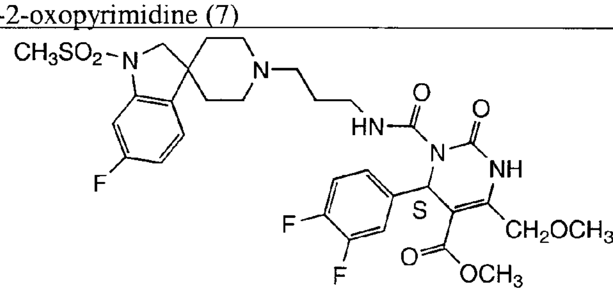
Analysis calc'd for C31H37F2N5O7S:

C,56.27; H,5.64; N, 10.58

Found: C,56.56; H,5.62; N, 10.26

EXAMPLE 7

1-{[3-(1,2-Dihydro-1-methanesulfonyl-6-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine (7)



The title compound was prepared according to the procedure described in Example 1 except 1,2-dihydro-1-methanesulfonyl-6-fluorospiro[3H-indole-3,4'-piperidine], which is prepared as described in US 5536716 , was substituted for spiro[1H-indeno-1,4'-piperidine] in step 1, and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in step 3. The freebase was obtained as an amorphous solid.

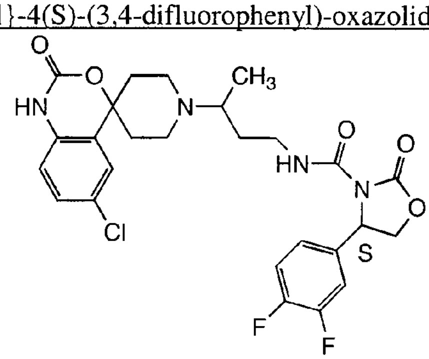
Analysis calc'd for C31H37F2N5O7S•0.25 C6H14(hexane) •C4H10O(ether):

C,55.71; H,5.72; N, 9.94

Found: C,55.74; H,5.67; N, 9.91

EXAMPLE 8

<u>3-{[3(R/S)-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one (**8**)</u>



<u>Step 1</u>: 1'-(1-cyanoprop-3(R/S)-yl)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidn]-2(1H)-one

A solution of 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (250 mg, 1.0 mmol) and crotononitrile (2ml) in methanol (10ml) was heated in a sealed tube for 96 hours. The methanol was removed under reduced pressure. The gum was purified by flash column chromatography eluting with 4% methanol/methylene chloride. The title compound was obtained as a white foam and used as is. NMR was consistent with structure. Mass spectra calculated for 319.793; Found 320.06.

Step 2: 1'-(1-Aminobut-3(R/S)-yl)- 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

A solution of 1'-(1-cyanoprop-3(R/S)-yl)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidn]-2(1H)-one(250mg, 0.78 mmol) in THF(5ml) was added to a 1M solution of lithium aluminium hydride in diethyl ether (1.8 ml) cooled to 0°C. The reaction mixture was stirred for one hour and then allowed to come to room temperature. After 1 hour at room temperature, the colorless solution had turned yellow and a solid precipitated. Ethyl acetate (5ml) was added and the reaction was cooled in an ice bath while water(1ml) was added. The suspension was filtered though filter cell and washed with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, filtered and concentrated to give 170mg of title compound as a white foamy solid which was used as is.

Step 3: 3-{[3(R/S)-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one

The title compound was prepared according to the procedure described in Example 1, Step 3, except 1'-(1-aminobut-3(R/S)-yl)- 6-chlorospiro[4H-3,1-benzox-azine-4,4'-piperidin]-2(1H)-one was substituted for 1'-(3-aminopropyl)spiro[1H-indeno-1,4'-piperidine]. The freebase was obtained as an amorphous solid.

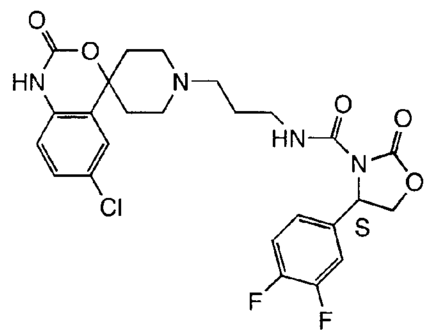
Analysis calc'd for C26H27ClF2N4O5:

C,56.89; H,4.96; N, 10.21

Found: C,56.84; H,5.35; N, 9.88

EXAMPLE 9

3-{[3-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one (**9**)



The title compound was prepared according to the procedure described in Example 1 except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] in Step 1. The acetate salt was obtained as an amorphous solid.

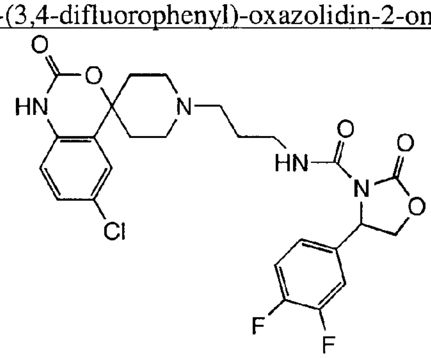
Analysis calc'd for $C_{25}H_{25}ClF_2N_4O_5 \cdot C_2H_4O_2 \cdot 1.6\ H_2O \cdot C_4H_{10}O$(ether):

C,52.56; H,5.58; N, 8.57

Found: C,52.53; H,5.20; N, 8.53

EXAMPLE 10

3-{[3-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one (**10**)



The title compound was prepared according to the procedure described in Example 1 except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] in Step 1 and racemic 4(R/S)-(3,4-difluorophenyl)-3-(4-nitrophenyl-oxycarbonyl)oxazolidin-2-one was substituted for

(+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in Step 3. The freebase was obtained as an amorphous solid.

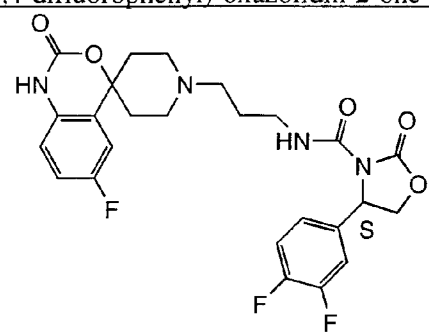
Analysis calc'd for C25H25ClF2N4O5•0.45 H2O•0.40 C4H10O(ether):

C,55.78; H,5.26; N, 9.78

Found: C,55.78; H,4.99; N, 9.40

EXAMPLE 11

3-{[3-(6-Fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one (**11**)



The title compound was prepared according to the procedure described in Example 1 except 6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] in Step 1. The freebase was obtained as an amorphous solid.

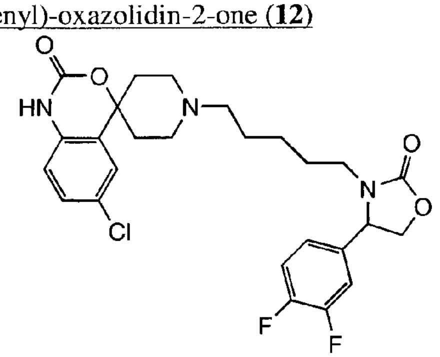
Analysis calc'd for C25H25F3N4O5•0.05 C6H14(hexane)•0.25 C4H10O(ether):

C,58.35; H,5.26; N, 10.35

Found: C,58.36; H,4.99; N, 10.33

EXAMPLE 12

3-{5-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one (**12**)



The title compound was prepared according to the procedure described in Example 1, step 1, except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] and racemic 4(R/S)-(3,4-difluorophenyl)-3-(5-bromopentyl)-oxazolidin-2-one was substituted for N-t-butoxycarbonyl-3-bromopropylamine. The freebase was obtained as an amorphous solid.

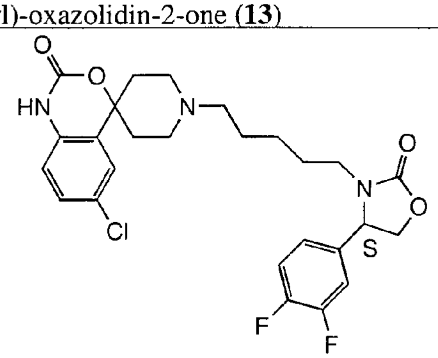
Analysis calc'd for $C_{26}H_{28}ClF_2N_3O_4$•0.1 H_2O•0.4 $C_4H_{10}O$(ether):

C,60.11; H,5.89; N, 7.62

Found: C,60.14; H,5.91; N, 7.65

EXAMPLE 13

3-{5-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one (**13**)



The title compound was prepared according to the procedure described in Example 1, step 1, except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] and 4(S)-(3,4-difluorophenyl)-3-(5-bromopentyl)-oxazolidin-2-one was substituted for N-t-butoxycarbonyl-3-bromopropylaminc. The freebase was obtained as an amorphous solid.

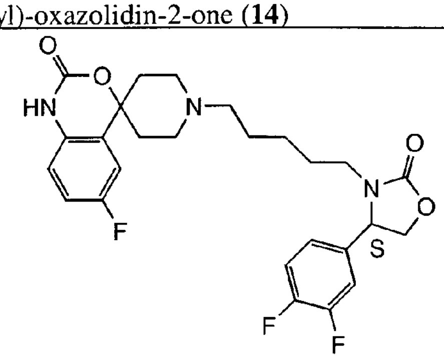
Analysis calc'd for C26H28ClF2N3O4:

C,60.06 H,5.43; N, 8.08

Found: C,59.93; H,5.79; N, 7.76

EXAMPLE 14

3-{5-(6-Fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one (**14**)



The title compound was prepared according to the procedure described in Example 1, step 1, except 6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] and 4(S)-(3,4-difluorophenyl)-3-(5-bromopentyl)-oxazolidin-2-one was substituted for N-t-butoxycarbonyl-3-bromopropylamine. The freebase was obtained as an amorphous solid.

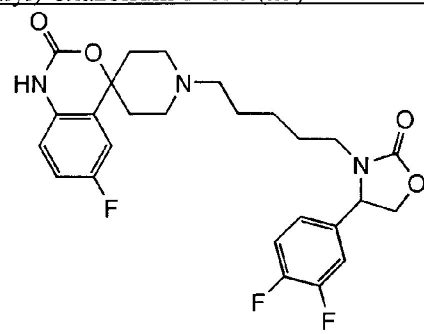
Analysis calc'd for C26H28F3N3O4•0.15 H2O:

C,61.68 H,5.64; N, 8.30

Found: C,61.66; H,5.83; N, 8.12

EXAMPLE 15

3-{5-(6-Fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one (**15**)



The title compound was prepared according to the procedure described in Example 1, step 1, except 6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] and racemic 4(R/S)-(3,4-difluorophenyl)-3-(5-bromopentyl)-oxazolidin-2-one was substituted for N-t-butoxycarbonyl-3-bromopropylamine. The freebase was obtained as an amorphous solid.

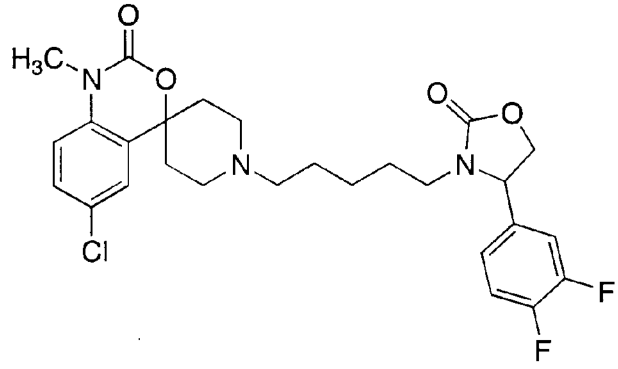
Analysis calc'd for $C_{26}H_{28}F_3N_3O_4 \cdot 0.45\ H_2O$:

C,61.69 H,5.93; N, 7.99

Found: C,61.70; H,5.93; N, 7.91

EXAMPLE 16

3-{5-(1-Methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one (**16**)



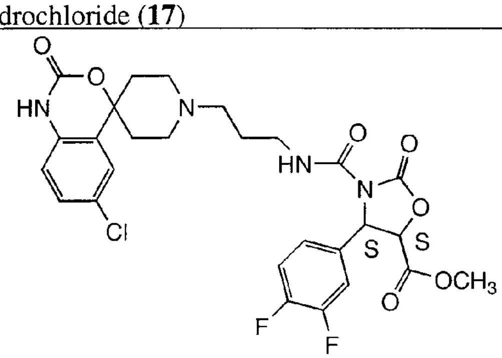
The title compound was prepared according to the procedure described in Example 1, step 1, except 1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one, which was prepared by methylation of the Boc-protected analog with methyl iodide and followed by deprotection with an acid (see Scheme 13), was substituted for spiro[1H-indeno-1,4'-piperidine] and racemic 4(R/S)-(3,4-difluorophenyl)-3-(5-bromopentyl)-oxazolidin-2-one was substituted for N-t-butoxy-carbonyl-3-bromo-propylamine. The freebase was obtained as an amorphous solid.

Analysis calc'd for C27H30ClF2N3O4:

	C,60.73; H,5.66; N, 7.87
Found:	C,60.83; H,5.69; N, 7.84

EXAMPLE 17

3-{[3-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-5(S)-methoxycarbonyl-oxazolidin-2-one Hydrochloride (**17**)



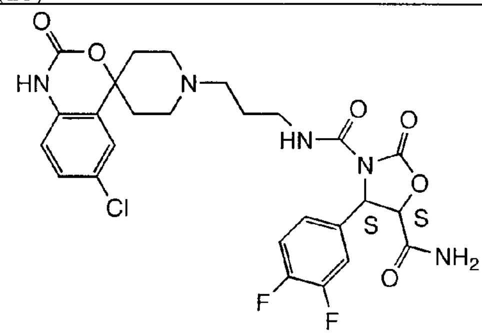
The title compound was prepared according to the procedure described in Example 1 except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[1H-indeno-1,4'-piperidine] in Step 1 and 5(S)-methoxycarbonyl-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyl-oxycarbonyl)oxazolidin-2-one was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in Step 3. The hydrochloride salt was obtained as an amorphous solid.

Analysis calc'd for C27H27ClF2N4O7•HCl• 0.75 H2O:

	C,50.43; H,4.62; N, 8.71
Found:	C,50.45; H,4.72; N, 8.54

EXAMPLE 18

3-{[3-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-5(S)-aminocarbonyl-oxazolidin-2-one Hydrochloride (**18**)



Solid 3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-5(S)-methoxycarbonyl-oxazolidin-2-one hydrochloride (195 mg, 0.31 mmol), from Example 17, was added to a suspension of silica gel (~600 mg) in chloroform(8 mL) saturated with ammonia gas in a ice bath. After stirring this suspension for one hour the solvent was removed under vacuum and the residue was chromatographed on a silica gel column eluting with a 0-3% methanol/ethyl acetate(satd. ammonia) gradient. The appropriate fractions were combined and the solvents removed. The residue was dissolved in ethyl acetate and treated with 1M HCl/ether and the hydrochoride salt of the title compound was isolated as an amorphous solid.

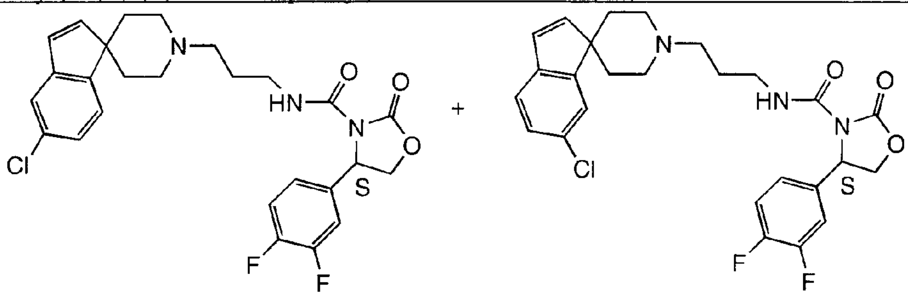
Analysis calc'd for C27H27ClF2N4O7•HCl• 0.85 H2O:

C,49.58; H,4.59; N, 11.12

Found: C,49.59; H,4.77; N, 10.85

EXAMPLE 19

1-{[3-(5- and 6-Monochloro-spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one **(19)**



The title compound mixture was prepared according to the procedure described in Example 1 except a mixture of 5- and 6-chloro-spiro[1H-indeno-1,4'-piperidine], which was prepared according to the method described in *J.Med. Chem.* 1992, 35, 2033-2039, was substituted for spiro[1H-indeno-1,4'-piperidine]. The hydrochloride salt of this mixture was obtained as an amorphous solid.

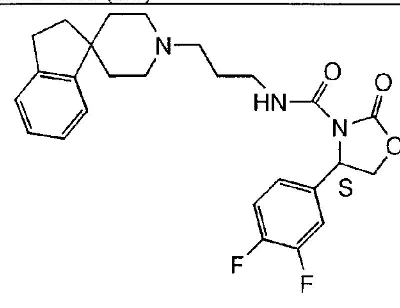
Analysis calc'd for C26H26ClF2N3O3•0.7 H2O•1.0 HCl:

C,56.67; H,5.20; N, 7.63

Found: C,56.68; H,5.27; N, 7.32

EXAMPLE 20

3-{[3-(Spiro[1H-indano-1,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one **(20)**



The title compound was prepared according to the procedure described in Example 1 except spiro[indano-1,4'-piperidine], which was prepared as described in *J.Med. Chem.* 1992, 35, 2033-2039, was substituted for spiro[1H-indeno-1,4'-piperidine]. The hydrochloride salt was obtained as a crystalline solid.

m.p.: 184-186°C.

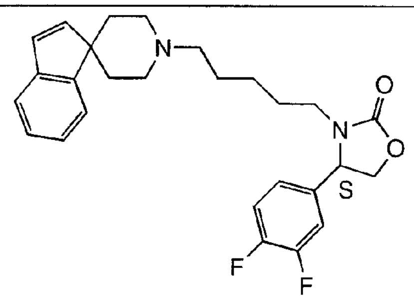
Analysis calc'd for C26H29F2N3O3•0.35 H2O•1.0 HCl:

C,60.95; H,6.04; N, 8.20

Found: C,60.98; H,5.97; N, 8.01

EXAMPLE 21

3-{5-(Spiro[1H-indeno-1,4'-piperidin]-1'-yl)pentyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one (**21**)



The title compound was prepared according to the procedure described in Example 1, Step 1, except 4(S)-(3,4-difluorophenyl)-3-(5-bromopentyl)-oxazolidin-2-one was substituted for N-t-butoxycarbonyl-3-bromopropylamine. The freebase was obtained as an amorphous solid.

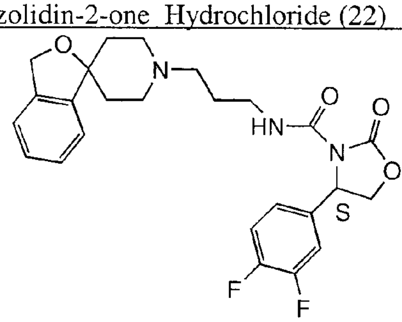
Analysis calc'd for C27H30F2N2O2•0.50 H2O:

C,70.26; H,6.77; N, 6.07

Found: C,70.26; H,6.44; N, 5.92

EXAMPLE 22

3-{[3-(Spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (22)



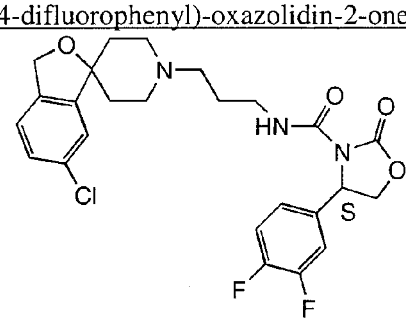
The title compound was prepared according to the procedure described in Example 1 except spiro[isobenzofuran-1(3H),4'-piperidine], which was prepared as described in *J.Org. Chem.* 1975, 40, 1427-1433, was substituted for spiro[1H-indeno-1,4'-piperidine] in step 1. The hydrochloride salt was obtained as an amorphous solid.

Analysis calc'd for C25H27F2N3O4•1.0 HCl:

	C,59.11; H,5.56; N, 8.27
Found:	C,58.85; H,5.50; N, 8.32

EXAMPLE 23

3-{[3-(6-Chloro-spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**23**)



The title compound was prepared according to the procedure described in Example 1 except 6-chloro-spiro[isobenzofuran-1(3H),4'-piperidine], which was prepared as described in *J.Org. Chem.* 1975, 40, 1427-1433, was substituted for spiro[1H-indeno-1,4'-piperidine] in step 1. The hydrochloride salt was obtained as a crystalline solid.

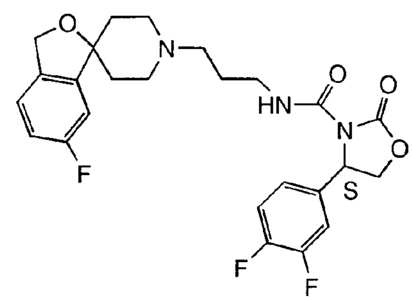
m.p.: 189-190°C.

Analysis calc'd for C25H26ClF2N3O4•1.0 HCl:

	C,59.11; H,5.56; N, 8.27
Found:	C,58.85; H,5.50; N, 8.32

EXAMPLE 24

3-{[3-(6-Fluoro-spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**24**)



The title compound was prepared according to the procedure described in Example 1 except 6-fluoro-spiro[isobenzofuran-1(3H),4'-piperidine], which was prepared as described in *J.Org. Chem.* 1975, 40, 1427-1433, was substituted for spiro[1H-indeno-1,4'-piperidine] in step 1. The hydrochloride salt was obtained as a crystalline solid.

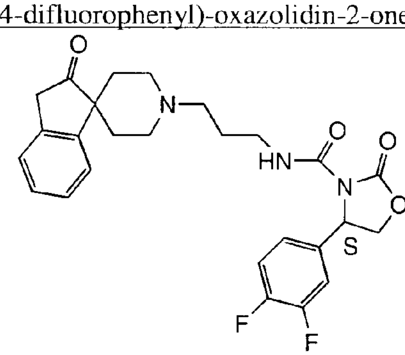
m.p.: 181-182°C.

Analysis calc'd for $C_{25}H_{26}F_3N_3O_4 \cdot 1.0\ HCl$:

	C,57.09; H,5.18; N, 7.99
Found:	C,56.80; H,4.97; N, 8.08

EXAMPLE 25

3-{[3-(2,3-Dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**25**)



Step 1: 1'-t-Butoxycarbonyl- 2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one

A solution of m-chloroperbenzoic acid (80%, 2.2 gm, 10 mmol) in chloroform (20 mL) was added to a solution of 1'-t- butylcarbonylspiro[1H-indeno-1,4'-piperidine] (2.0 gm, 7 mmol) in chloroform((30 mL) containing powdered

potassium carbonate (6.5 gm). This mixture was stirred at r.t. for 24 to 48 hours monitoring the reaction progress by TLC. Additional peracid was added if needed. The mixture was diluted with ethyl acetate and the organic layer washed with aq. sodium carbonate and water, dried and the solvent evaporated under vacuum. The crude 1'-t-butoxycarbonyl-2,3-epoxy-2,3 dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one was dissolved in methylene chloride (25 mL) and four drops of boron trifluoride etherate was added to catalyze the epoxide rearrangement. After stirring for one hour, the solution was washed with aq. sodium carbonate and the solvent evaporated. The residue was chromatographed on a silica gel column eluting with a 5 –15% ethyl acetate/hexane gradient to give the title compound as a solid which crystallized from cold hexane.

m.p.: 80-82°C.

Step 2: 2,3-Dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one

A solution of 1'-t-butoxycarbonyl- 2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)one (212 mg, 0.7 mmol) in chloroform (5 mL) containing trifluoroacetic acid (0.2 mL) was stirred at r.t. for 15 hours. The reaction mixture was washed with aq. sodium carbonate and the organic layer dried, filtered and evaporated to give the title compound as an oil which was used as is.

Step 3: 3-{[3-(2,3-Dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one

The title compound was prepared according to the procedure described in Example 1 except 2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one was substituted for spiro[1H-indeno-1,4'-piperidine]. The hydrochloride salt was obtained as an amorphous solid.

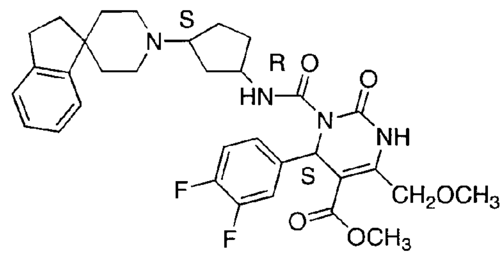
Analysis calc'd for C26H27F2N3O4•1.0 HCl•0.70H2O:

C,58.63; H,5.56; N, 7.89

Found: C,58.65; H,5.59; N, 7.88

EXAMPLE 26

1-{*cis*-[3(S)-(Spiro[indano-1,4'-piperidin]-1'-yl)cyclopent-1(R)-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride (**26**)



Step 1: 1'-(*cis*-3(R)-t-Butoxycarbonylaminocyclopent-1(S)-yl)-spiro[indano-1,4'-piperidine] and 1'-(*trans*-3(R)-t-butoxycarbonylaminocyclopent-1(R)-yl)-spiro[indano-1,4'-piperidine]

A solution of spiro[indano-1,4'-piperidine] (260 mg, 1.39 mmol) and 3(R)-t-butoxycarbonylaminocyclopentan-3-one (189 mg, 0.95 mmol), which can be prepared as described in WO 99/25345, in methanol (5 mL) containing acetic acid (0.23 mL, ~1.0 mmol) was stirred for fifteen minutes and then sodium cyanoborohydride (70 mg, 1.1 mmol) was added and the reaction stirred at r.t. for 15 hours. The reaction was diluted with ethyl acetate, the organic layer washed with saturated aq. sodium carbonate, dried and the solvent evaporated. The residue was chromatographed on a silica gel column eluting with a 70 – 100% ethyl acetate/hexane gradient. The first product to elute was the *cis* isomer and the second product was the *trans* isomer. Each was used as is.

Step 2: 1-{*cis*-[3(S)-(Spiro[indano-1,4'-piperidin]-1'-yl)cyclopent-1(R)-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride

The title compound was prepared according to the procedure described in Example 1, beginning with Step 2, except 1'-(*cis*-3(R)-t-butoxycarbonylamino-cyclopent-1(S)-yl)-spiro[indano-1,4'-piperidine] was substituted for 1'(3-t-butoxycarbonylamino-propyl)-spiro[1H-indeno-1,4'-piperidine] in Step 2, and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in Step 3. The hydrochloride salt was obtained as a crystalline solid.

m.p.: 208-210°C.

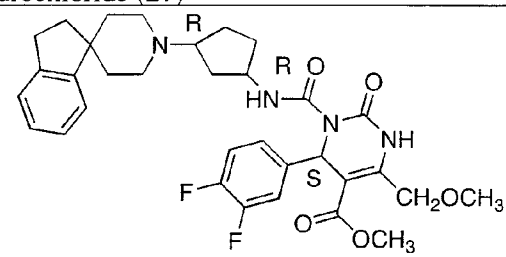
Analysis calc'd for C33H38F2N4O5•1.0 HCl:

C,61.43; H,6.09; N, 8.69

Found: C,61.19; H,6.13; N, 8.62

EXAMPLE 27

1-{*trans*-[3(R)-(Spiro[indano-1,4'-piperidin]-1'-yl)cyclopent-1(R)-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride (**27**)



The title compound was prepared according to the procedure described in Example 1, beginning with Step 2, except 1'-(*trans*-3(R)-t-butoxycarbonylamino-cyclopent-1(R)-yl)-spiro[indano-1,4'-piperidine] from Example 26, Step 1, was substituted for 1'-(*cis*-3(R)-t-butoxycarbonylaminocyclopent-1(S)-yl)-spiro[indano-1,4'-piperidine], and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in Step 3. The hydrochloride salt was obtained as an amorphous solid.

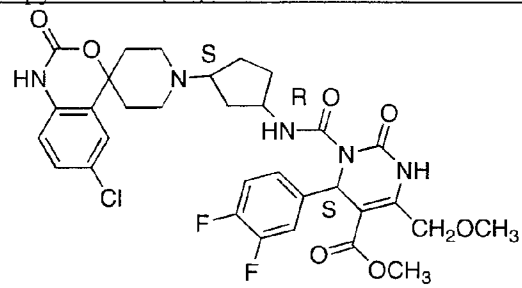
Analysis calc'd for $C33H38F2N4O5 \bullet 1.0\ HCl \bullet 0.30\ H2O$:

C,60.92; H,6.14; N, 8.61

Found: C,60.96; H,6.08; N, 8.39

EXAMPLE 28

1-{[*cis*-[3(S)-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclopent-1(R)-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine (**28**)



The title compound was prepared according to the procedure described in Example 26, except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one which is prepared as described in *J.Med. Chem.* 1983, 26, 657-661, was substituted for spiro[indano-1,4'-piperidine] in Step 1. The hydrochloride salt was obtained as an amorphous solid.

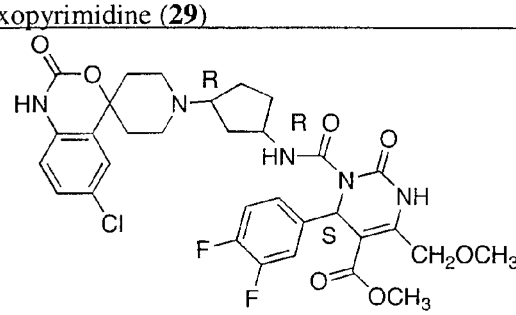
Analysis calc'd for C32H34ClF2N5O7•1.0 HCl•0.55 H2O:

C,53.34; H,5.05; N, 9.72

Found: C,53.32; H,5.14; N, 9.94

EXAMPLE 29

1-{[*trans*-[3(R)-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclopent-1(R)-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine (**29**)



The title compound was prepared according to the procedure described in Example 1, beginning with Step 2, except 1'-(*trans*-3(R)-aminocyclopent-1(R)-yl)-

6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one from Example 28 was substituted for 1'-(*cis*-3(R)-aminocyclopent-1(S)-yl)- spiro[indano-1,4'-piperidine] in Step 2, and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in Step 3. The hydrochloride salt was obtained as an amorphous solid.

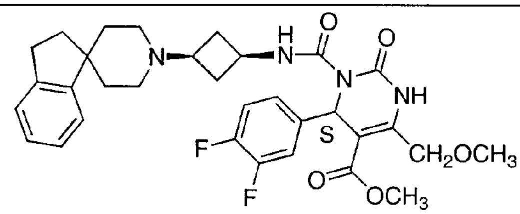
Analysis calc'd for $C_{32}H_{34}ClF_2N_5O_7$•1.0 HCl•0.35 H_2O:

C,53.61; H,5.02; N, 9.77

Found: C,53.57; H,4.90; N, 9.95

EXAMPLE 30

<u>1-{[*cis*-3-(Spiro[indano-1,4'-piperidin]-1'-yl)cyclobut-1-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride **(30)**</u>



<u>Step 1</u>: 3,3-Dimethoxy-cyclobutanecarboxylic acid

A solution of methyl 3,3-dimethoxy-cyclobutane carboxylate (875 mg, 5 mmol) , which was prepared as described in *J. Org. Chem.*1996, <u>61</u>, 2174-2178, in tetrahydrofuran (8 mL) and water (2 mL) containing lithium hydroxide monohydrate (105 mg, 2 mmol) was stirred for fifteen hours. The solvents were evaporated and the residue dissolved in water. The aqueous solution was washed with diethyl ether and then acidified with 2 <u>N</u> HCl. The product was extracted into diethyl ether, the solvent dried, filtered and evaporated to the give product (397 mg, 49% yield) as a semi-solid which was used as is.

<u>Step 2</u>: 3-(t-Butoxycarbonylamino)cyclobutanone

The crude 3,3-dimethoxy-cyclobutane carboxylic acid (420 mg, 2.6 mmol) was dissolved in dry benzene (6 mL) containing triethylamine (0.42 mL, 3 mmol) and then diphenylphosphorylazide (0.59 mL, 2.75 mmol) was added dropwise. The reaction was heated at 75°C for 2.5 hours. The cooled reaction was diluted with

ethyl acetate. The organic layer was washed with aq. sodium carbonate, dried, filtered and evaporated to give the crude isocyanate which was a lacrimator. This material was dissolved in anhydrous t-butyl alcohol (4 mL) and heated at 80°C for seventeen hours. The cooled reaction was diluted with ethyl acetate and washed with water twice, dried and the solvent removed under vacuum. The crude 1-(t-butoxycarbonylamino)-3,3-dimethoxycyclobutane was dissolved in acetone (5 mL) and water (2 mL) to which 2 N HCl (0.5 mL) was added and the solution stirred at r.t. for three hours. The product was extracted into ethyl acetate, the extract washed with water, dried, filtered and evaporated. The residue was triturated with diethyl ether to give the title compound as a solid.

Step 3: 1-{*cis*-[3-(Spiro[indano-1,4'-piperidin]-1'-yl)cyclobut-1-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride

The title compound was prepared according to the procedure described in Example 26, except 3-(t-butoxycarbonylamino)cyclobutanone was substituted for 3(R)-t-butoxycarbonylaminocyclopentan-3-one in Step 1. The hydrochloride salt was obtained as a crystalline solid.

m.p.: >260°C.

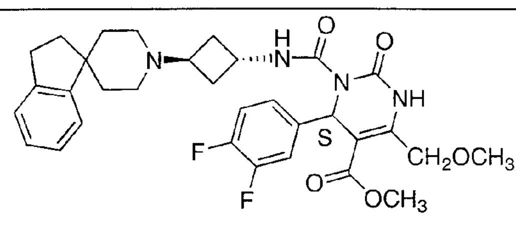
Analysis calc'd for C1H34F2N4O4•1.0 HCl•0.40 H2O:

C,61.20; H,5.93; N, 9.21

Found: C,61.19; H,5.86; N, 9.54

EXAMPLE 31

1-{[*trans*-3-(Spiro[indano-1,4'-piperidin]-1'-yl)cyclobut-1-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride (**31**)



The title compound was prepared according to the procedure described in Example 1, beginning with Step 2, except 1'-(*trans*-3-aminocyclobut-1-

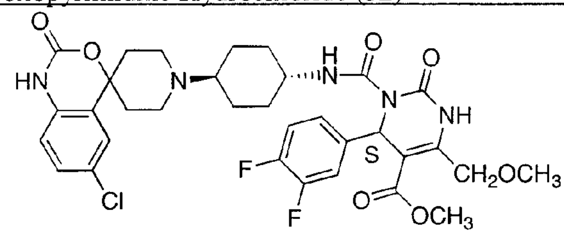
yl)spiro[indano-1,4'-piperidine] from Example 30, Step 3 was substituted for 1'-(*cis*-3(R)-aminocyclo-pent-1(S)-yl)-spiro[indano-1,4'-piperidine] in Step 2, and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in Step 3. The hydrochloride salt was obtained as an amorphous solid.

Analysis calc'd for C31H34F2N4O4•1.0 HCl•0.60 H2O:

	C,60.84; H,5.96; N, 9.16
Found:	C,60.84; H,5.95; N, 9.09

EXAMPLE 32

1-{[*trans*-4-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclohex-1-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride (**32**)



Step 1: 1'-(4-Oxo-1-cyclohexyl)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

A solution of 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (759 mg, 3 mmol) and 1,4-cyclohexanedione monoethylene ketal (1.9 g, 12 mmol) in 1,2-dichloroethane (15 mL) containing acetic acid (~3 mL) was stirred for fifteen minutes and then sodium triacetoxyborohydride (690 mg, 3.25 mmol) was added and the reaction stirred at r.t. for 3-5 days periodically adding more 1,4-cyclohexanedione monoethylene ketal (1.48 g, 9.3 mmol) and sodium triacetoxyborohydride (1.11 g, 5.2 mmol) while monitoring reaction progress by tlc. The reaction was diluted with methanol and aq. sodium carbonate. The product was extracted into chloroform, dried and the solvents evaporated. The residue was triturated with diethyl ether and the solid product ketal collected by filtration.

m.p.: 259-262°C.

This ketal was dissolved in dimethylethylene glycol (12 mL) and 1 N HCl (6 mL) and heated at 70°C for one hour. The cooled reaction was quenched carefully with aq. sodium carbonate and the product extracted into chloroform/methanol, dried, filtered and the solvents evaporated. The residue was triturated with diethyl ether and the title compound was collected as a solid. m.p.: 234-237°C.

Step 2: 1'-(*cis* and *trans*-4-amino-1-cyclohexyl)-6-chlorospiro[4H-3,1-benzoxazine-4,4-piperidin]-2(1H)-one

A solution of 1'-(4-oxo-1-cyclohexyl)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (714 mg, 2.05 mmol) and ammonium acetate (1.54 g, 20 mmol) in methanol (20 mL) containing acetic acid (~1 mL) was stirred for three hours and then sodium cyanoborohydride (138 mg, 2.2 mmol) was added and the reaction was stirred for an additional 1.5 hours. Aqueous sodium carbonate and sodium hydroxide were added and the crude product was exhaustively extracted into chloroform/methanol. This extract was dried and the solvents evaporated. The residue was triturated with diethyl ether/acetonitrile to give a mixture of *cis* and *trans* products. This material was chromatographed on a silica gel column eluting with a 5-14% methanol/chloroform(sat'd with ammonium hydroxide) gradient. The appropriate fractions were combined, the solvents evaporated and the residue digested in acetonitrile to give each isomer as a solid. The first to elute was the *cis* isomer and the second was the *trans* isomer.

Step 3: 1-{[*trans*-4-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclohex-1-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxy-methyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride

The title compound was prepared according to the procedure described in Example 1, Step 3, except 1'-(*trans*-4-amino-1-cyclohexyl)-6-chlorospiro[4H-3,1-benzoxazine-4,4-piperidin]-2(1H)-one was substituted for 1'-(3-aminopropyl)-spiro[1H-indeno-1,4'-piperidine], and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one. The hydrochloride salt was obtained as a crystalline solid.

m.p.: 210-213°C.

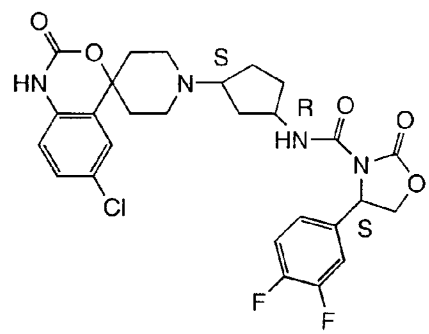
Analysis calc'd for C33H36ClF2N5O7•1.0 HCl•0.40 H2O:

C,54.16; H,5.21; N, 9.57

Found: C,54.19; H,5.08; N, 9.28

EXAMPLE 33

3-{[*cis*-3(S)-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one **(33)**



The title compound was prepared according to the procedure described in Example 1, Step 3 except 1'-(*cis*-3(R)-aminocyclopent-1(S)-yl)-6-chloro-spiro[4H-3,1-benzoxazine-4,4-piperidin]-2(1H)-one from Example 28 was substituted for 1'-(3-aminopropyl)-spiro[1H-indeno-1,4'-piperidine]. The freebase was obtained as a crystalline solid.

m.p.: 188-190°C.

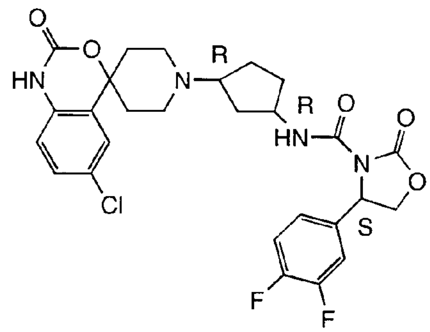
Analysis calc'd for C27H27ClF2N4O5:

C,57.81; H,4.85; N, 9.99

Found: C,57.48; H,5.08; N, 10.18

EXAMPLE 34

3-{[*trans*-3(R)-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one **(34)**



The title compound was prepared according to the procedure described in Example 1, Step 3 except 1'-(*trans*-3(R)-aminocyclopent-1(R)-yl)-6-chloro-spiro[4H-3,1-benzoxazine-4,4-piperidin]-2(1H)-one from Example 28 was substituted for 1'-(3-aminopropyl)-spiro[1H-indeno-1,4'-piperidine]. The freebase was obtained as an amorphous solid.

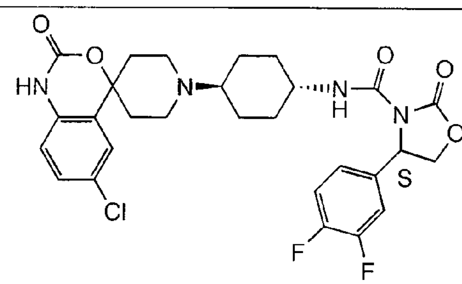
Analysis calc'd for C27H27ClF2N4O5•H2O:

C,56.89; H,4.95; N, 9.83

Found: C,56.87; H,4.96; N, 10.05

EXAMPLE 35

3-{[*trans*-4-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**35**)

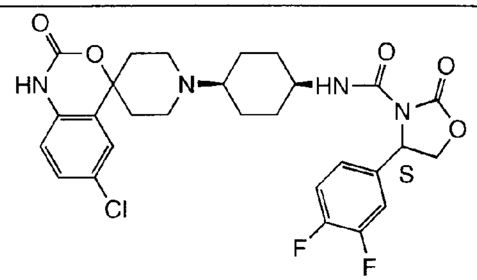


The title compound was prepared according to the procedure described in Example 1, Step 3 except 1'-(*trans*-4-aminocyclohex-1-yl)-6-chloro-spiro[4H-3,1-benzoxazine-4,4-piperidin]-2(1H)-one from Example 32, Step 2 was substituted for 1'-(3-aminopropyl)-spiro[1H-indeno-1,4'-piperidine]. The hydrochloride salt was obtained as an amorphous solid.

Analysis calc'd for C28H29ClF2N4O5•HCl•0.55H2O:
C,54.12; H,5.04; N, 9.02
Found: C,54.14; H,5.04; N, 8.99

EXAMPLE 36

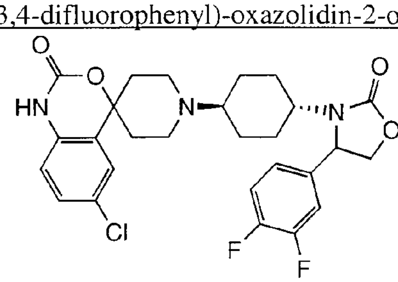
3-{[*cis*-4-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**36**)



The title compound was prepared according to the procedure described in Example 1, Step 3 except 1'-(*cis*-4-aminocyclohex-1-yl)-6-chloro-spiro[4H-3,1-benzoxazine-4,4-piperidin]-2(1H)-one from Example 32, Step 2 was substituted for 1'-(3-aminopropyl)-spiro[1H-indeno-1,4'-piperidine]. The hydrochloride salt was obtained as an crystalline solid
m.p.: 226-228°C.
Analysis calc'd for C28H29ClF2N4O5•HCl:
C,55.00; H,4.95; N, 9.16
Found: C,54.97; H,4.89; N, 8.99

EXAMPLE 37

(3-{*trans*-4-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl}- 4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**37**)



Step 1: 1'-[*cis/trans* -4-(2-hydroxy-1(R/S)-(3,4-difluorophenyl)ethylamino)-1-cyclohexyl]-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

A solution of 1'-(4-oxo-1-cyclohexyl)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (348 mg, 1 mmol) from Example 32, Step 1, and racemic 2-(3,4-difluorophenyl)-2-aminoethanol (260 mg, 1.5 mmol) in 1,2-dichloroethane (6 mL) containing acetic acid (~2.5 mL) was stirred for fifteen minutes and then sodium triacetoxyborohydride (246 mg, 1.16 mmol) was added and the reaction stirred at r.t. for four hours. The reaction was diluted with chloroform and washed with aq. sodium carbonate. The chloroform extract was dried, filtered and the solvent evaporated. The residue was triturated with diethyl ether and the solid isomeric product mixture was collected by filtration.

Step 2: 3-{*trans*-4-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl}- 4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride

A suspension of 1'-[*cis/trans*-4-(2-hydroxy-1(R/S)-(3,4-difluorophenyl)-ethylamino)-1-cyclohexyl]-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (487 mg, 0.96 mmol) in chloroform (10 mL) and ethyl acetate (5 mL) containing triethylamine (0.28 mL, 2 mmol) was stirred as phosgene (20% in toluene, ~2 mL) was added dropwise monitoring by tlc until the reaction was complete. The reaction mixture was diluted with chloroform and washed with aq. sodium carbonate. The chloroform layer was dried, filtered and the solvent evaporated. The residue was chromatographed on a silica gel column eluting first with a 50-100% ethyl acetate gradient and then a 1-4% methanol/ethyl acetate(sat'd with ammonium hydroxide) gradient. The first product to elute was the *cis* isomer and the second the *trans* isomer. The *trans* isomer was converted to its hydrochloride salt to give the title compound as an amorphous solid.

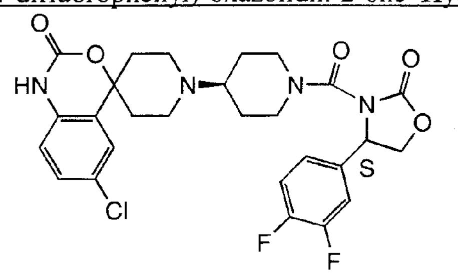
Analysis calc'd for $C_{27}H_{28}ClF_2N_3O_4$•HCl•0.35 H_2O:

C,56.42; H,5.21; N, 7.31

Found: C,56.44; H,5.32; N, 7.24

EXAMPLE 38

3-{[4-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-piperidin-1-yl]carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**38**)



Step 1: 1'-(1-t-Butoxycarbonylpiperidin-4-yl)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

The title compound was prepared according to the procedure described in Example 32, Step 1, except N-t-butoxycarbonyl-4-piperidinone was substituted for 1,4-cyclohexanedione monoethylene ketal. The crude product was chromatographed on a silica gel column eluting with a 50-100% ethyl acetate/hexane gradient. The appropriate fractions were combined , the solvents evaporated and the residue triturated with diethyl ether to give the title compound as a solid.

Step 2: 3-{[4-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-piperidin-1-yl]carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride

The title compound was prepared according to the procedure described in Example 1, beginning with Step 2, except 1'-(1-t-Butoxycarbonylpiperidin-4-yl)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one was substituted for 1'-(3-t-butoxycarbonylaminopropyl)-spiro[1H-indeno-1,4'-piperidine] in Step 2. The hydrochloride salt was obtained as an crystalline solid.

m.p.: 239-241°C.

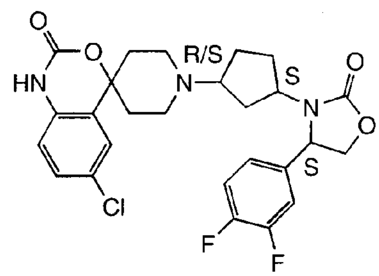
Analysis calc'd for $C27H27ClF2N4O5 \bullet HCl \bullet H2O$:

C,53.39; H,4.83; N, 9.23

Found: C,53.33; H,4.68; N, 9.62

EXAMPLE 39

3-{*cis/trans*-3(R/S)-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(S)-yl}- 4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride **(39)**



Step 1: 4(S)-(3,4-difluorophenyl)-3-(cyclopenten-3(S)-yl)-oxazolidin-2-one

A solution of 2.5 M n-butyl lithium in tetrahydrofuran (1.7 mL, 4.25 mmol) was added dropwise to a solution of (+)-4(S)-(3,4-difluorophenyl)oxazolidin-2-one (820 mg, 4.1 mmol) in dry tetrahydrofuran (10 mL) cooled to -70°C under an argon atmosphere. Palladium tetrakis(triphenylphoshine) (10 mg) was added to this suspension followed by a solution of 3-benzoyloxycyclopentene (900 mg, 4.7 mmol), which was prepared as described in *J. Org. Chem.* 1992, 57, 729-740, in tetrahydrofuran (5 mL). This reaction mixture was heated at 60°C for 5-7 hours. The reaction was cooled and diluted with ethyl acetate and washed with aq. sodium carbonate. The organic layer was dried, filtered and evaporated. The residue was chromatographed on a silica gel column eluting with a 20-70% ethyl acetate/hexane gradient. The appropriate fractions were combined and the solvents removed under vacuum to give a ~2:1 mixture of diastereo-mers as determined by NMR (897mg, 82% yield). This material was used as is in the next step. Upon standing the major diastereomer crystallized out and was collected. Recrystal-lization from hexane/diethyl ether afforded pure title compound as needles, mp: 80-82°C. From an x-ray diffraction study the absolute configuration at C-3 of the cyclopentene ring was determined to be S.

Step 2: 4(S)-(3,4-difluorophenyl)-3-(3-oxo-cyclopent-1(S)-yl)-oxazolidin-2-one

Solid N-bromosuccinimide (625 mg, 3.5 mmol) was added in portions to a solution of diastereomeric 4(S)-(3,4-difluorophenyl)-3-(cyclopenten-3(S/R)-yl)-oxazol-idin-2-ones (732 mg, 2.76 mmol) in dimethylsulfoxide (3 mL) containing

water (0.18 mL, 10 mmol) which was cooled in an ice bath. After stirring at r.t. for fifteen hours, aq. sodium bicarbonate was added and the crude bromohydrin product mixture was extracted into ethyl acetate. This extract was dried, filtered and the solvent removed. This material (1.07 g, ~2.7 mmol) was dissolved in dry benzene (15 mL) and tri(n-butyl)tin hydride (1.7 mL, ~6 mmol) was added. 2,2'-Azobisisobutyronitrile (AIBN, 10 mg) was added as a radical initiator and the reaction mixture was heated at 80°C for fifteen hours. The solvent was evaporated under vacuum and the residue was chromatographed on a silica gel column eluting first with a 35-100% ethyl acetate/hexane gradient and then a 1-3% methanol/ethyl acetate. The appropriate fractions were combined and the solvents evaporated to give a mixture of 3-cyclopentane alcohols (475 mg). This material was dissolved in methylene chloride (35 mL) and a filter aid such as Celite (2.6 g) was added, followed by pyridinium chlorochromate (527 mg, 2.4 mmol). After stirring at r.t. for five hours, diethyl ether (35 mL) was added and the suspended material removed by filtration. The solvents were evaporated and the residue was taken up in ethyl acetate and this solution passed through a short plug of silica gel to remove residual chromium salts. Evaporation of the solvent afforded the product as a mixture of diastereomeric ketones (362 mg, 46% overall yield). This material was chromatographed on a chiral Chiralpak OD column eluting with 75% hexane(containing 0.1% diethyl amine)/25% ethanol. The first diastereomer to elute was 4(S)-(3,4-difluorophenyl)-3-(3-oxo-cyclopent-1(R)-yl)-oxazolidin-2-one and the second was the title compound 4(S)-(3,4-difluorophenyl)-3-(3-oxo-cyclopent-1(S)-yl)-oxazolidin-2-one. The latter stereochemical assignment was confirmed when the product obtained from a pure sample of 4(S)-(3,4-difluorophenyl)-3-(cyclopenten-3(S)-yl)-oxazolidin-2-one, from Step 1, submitted to the above reaction sequence was shown to be identical on a chiral column.

<u>Step 3</u>: 3-{*cis/trans*-3(R/S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(S)-yl}- 4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride

A solution of 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H) one (85 mg, 0.33 mmol) and 4(S)-(3,4-difluorophenyl)-3-(3-oxo-cyclopent-1(S)-yl)-oxazolidin-2-one (78 mg, 0.28 mmol) in methanol (5 mL) containing acetic acid (0.06 mL, ~1.0 mmol) was stirred for fifteen minutes and then sodium cyanoborohydride (28 mg, 0.43 mmol) was added. The reaction was stirred at r.t. for 15 hours. After diluting the reaction with ethyl acetate, the organic layer was separated and washed

with saturated aq. sodium carbonate, dried and the solvent evaporated. The residue was chromatographed on a silica gel column eluting first with a 50 – 100% ethyl acetate/hexane gradient and then a 0.5-1% methanol/ethyl acetate gradient. The appropriate fractions were combined and the solvents evaporated to give the product as a mixture of *cis/trans* isomers. This was converted to an amorphous hydrochloride salt.

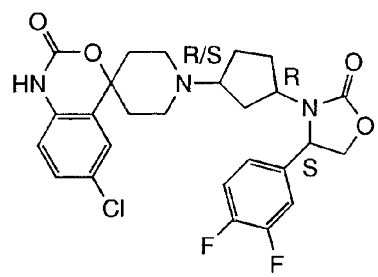
Analysis calc'd for C26H26ClF2N3O4•HCl•0.40 H2O:

C,55.60; H,4.99; N, 7.48

Found: C,55.59; H,4.96; N, 7.09

EXAMPLE 40

3-{*cis/trans*-3(R/S)-(6-Chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl}- 4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride **(40)**



The title compound was prepared according to the procedure described in Example 39, Step 3, except 4(S)-(3,4-difluorophenyl)-3-(3-oxo-cyclopent-1(R)-yl)-oxazolidin-2-one from Example 39, Step 2, was substituted for 4(S)-(3,4-difluorophenyl)-3-(3-oxo-cyclopent-1(S)-yl)-oxazolidin-2-one. The hydrochloride salt of this *cis/trans* mixture was obtained as an amorphous solid.

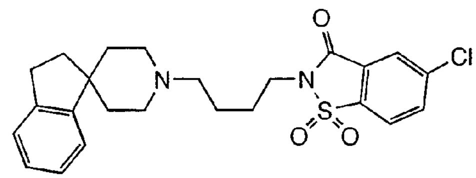
Analysis calc'd for C26H26ClF2N3O4•1.0 HCl•1.0 H2O:

C,54.55; H,5.11; N, 7.34

Found: C,54.49; H,4.96; N, 7.33

EXAMPLE 41

1,1-Dioxido-2-[4-(spiro[indano-1,4'-piperidin]-1'-yl)butyl]-5-chloro-1,2-benzisothiazol-3(2H)-one **(41)**



The title compound was prepared according to the procedure described in Example 1, Step 1 except spiro[indano-1,4'-piperidine], which is prepared as described in *J.Med. Chem.* 1992, 35, 2033-2039 , was substituted for spiro[1H-indeno-1,4'-piperidine] and 1,1-dioxido-2-(4-bromobutyl)-5-chloro-1,2-benzisothiazol-3(2H)-one was substituted for N-t-butoxycarbonyl-3-bromopropylamine. The hydrochloride salt was obtained as a crystalline solid.

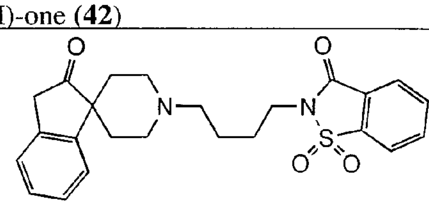
m.p.: 256-258°C.

Analysis calc'd for $C_{24}H_{27}ClN_2O_3S \cdot 1.0\ HCl$:

	C,58.18; H,5.70; N, 5.66
Found:	C,58.14; H,5.77; N, 5.02

EXAMPLE 42

1,1-Dioxido-2-[4-(2,3-dihydrospiro[1H-indeno-1,4'-piperidin]-2(3H)on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one (**42**)



The title compound was prepared according to the procedure described in Example 1, Step 1 except 2,3-dihydrospiro[1H-indeno-1,4'-piperidin]-2(3H)one, from Example 25, Step 2, was substituted for spiro[1H-indeno-1,4'-piperidine] and 1,1-di-oxido-2-(4-bromobutyl)-1,2-benzisothiazol-3(2H)-one was substituted for N-t-butoxy-carbonyl-3-bromopropylamine. The hydrochloride salt was obtained as a crystalline solid.

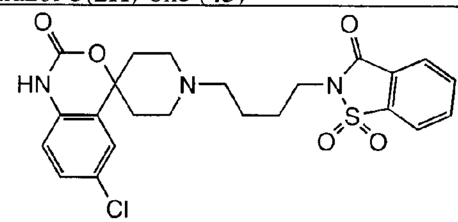
m.p.: 165-167°C.

Analysis calc'd for $C_{24}H_{26}N_2O_4S \cdot 1.0\ HCl \cdot 0.30\ H_2O$:

	C,60.00; H,5.79; N, 5.83
Found:	C,60.04; H,5.81; N, 5.81

EXAMPLE 43

1,1-Dioxido-2-[4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one (**43**)



The title compound was prepared according to the procedure described in Example 1, Step 1 except 6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one, which is prepared as described in *J. Med. Chem.* 1983, 26,657-661, was sub-stituted for spiro[1H-indeno-1,4'-piperidine] and 1,1-dioxido-2-(4-bromobutyl)-1,2-benzisothiazol-3(2H)-one was substituted for N-t-butoxy-carbonyl-3-bromopropylamine. The freebase was obtained as a crystalline solid.

m.p.: 208-210°C.

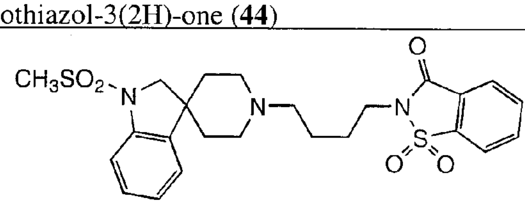
Analysis calc'd for C23H24ClN3O5S:

C,56.38; H,4.94; N, 8.58

Found: C,56.25; H,5.00; N, 8.49

EXAMPLE 44

1,1-Dioxido-2-[4-(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one (**44**)



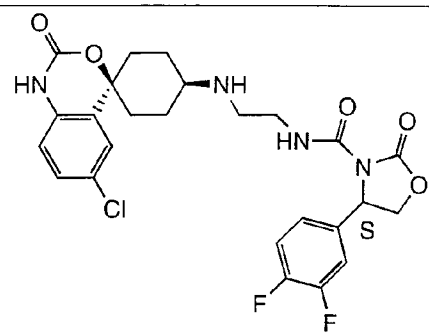
The title compound was prepared according to the procedure described in Example 1, Step 1 except 1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidine], which is prepared as described in US 5536716, was substituted for spiro[1H-indeno-1,4'-piperidine] and 1,1-di-oxido-2-(4-bromobutyl)-1,2-

benzisothiazol-3(2H)-one was substituted for N-t-butoxy-carbonyl-3-bromopropylamine. The freebase was obtained as a crystalline solid.
m.p.: 143-144°C.
Analysis calc'd for C24H29N3O5S2:

	C,56.53; H,5.87; N, 8.24
Found:	C,56.51; H,5.68; N, 8.09

EXAMPLE 45

3-{[2-(*cis*-6-Chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**45**)



Step 1: 6-Chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H),1'-dione

A solution of 1.7 M t-butyl lithium/pentane (14 mL, 23.8 mmol) was added dropwise to a solution of N-t-butoxycarbonyl-4-chloroaniline (2.39 g, 10.5 mmol) in dry tetrahydrofuran (40 mL) containing bipyridyl (10 mg) as an endpoint indicator which was cooled to -70°C under an argon atmosphere. The light reddish-amber solution was allowed to warm to -20°C over one hour to give a brownish colored solution which was maintained at that temperature for two more hours. The reaction was then re-cooled to - 70°C and a solution of 1,4-cyclohexanedione mono-2,2-dimethyltrimethylene ketal (2.04 g, 10.3 mmol) in tetrahydrofuran (30 mL) was added dropwise and then warmed slowly to r.t. over twelve hours. The reaction was quenched with 2 N HCl, and the product extracted into ethyl acetate. This extract was dried, filtered and the solvent evaporated. The residue was triturated with diethyl ether to give the ketal product as a crystalline solid (919 mg, 25% yield), mp: >260°C. This material was suspended in dimethylethylene glycol (20 mL) and 1 N HCl (10

mL) and heated at 80°C for 1.3 hours. The solution was diluted with water as the product slowly crystallized out. The title compound was obtained as a tan solid. m.p.: 248-250°C.

<u>Step 2</u>: *cis* and *trans*-1'-(2-Aminoethylamino)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-one

A suspension of 6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H),1'-dione (461 mg, 1.73 mmol) in dry benzene (20 mL) containing ethylenediamine (0.35 mL, 5 mmol) and a catalytic amount of p-toluenesolfonic acid monohydrate(20 mg) was refluxed for two hours with a Dean-Stark watertrap. The solvent was removed under vacuum and the residue dissolved in methanol (10 mL) and sodium cyanoborohydride (130 mg, 2 mmol) was added along with a few drops of acetic acid. The reaction was stirred at r.t. for fifteen hours and then the solvent was removed under vacuum and the residue partitioned between ethyl acetate and 2 <u>N</u> HCl. The aqueous layer was made basic with aq. sodium carbonate/sodium hydroxide and the crude product mixture extracted into chloroform. This extracted was dried, filtered and evaporated and the residue was chromatographed on a silica gel column eluting with 10 –20% methanol/ chloroform(saturated with ammonia). The first isomer to elute was the *trans*-1'-(2-amino-ethylamino)-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-one and the second isomer to elute was *cis*-1'-(2-amino-ethylamino)-6-chloro-spiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-one. Both were oils and were used as is.

<u>Step 3:</u> 3-{[2-(*cis*-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride

The title compound was prepared according to the procedure described in Example 1, Step 3 except *cis*-1'-(2-aminoethylamino)-6-chloro-spiro[4H-3,1-benzoxa-zine-4,4'-cyclohexan]-2(1H)-one was substituted for 1'-(3-aminopropyl)-spiro[1H-indeno-1,4'-piperidine]. The hydrochloride salt was obtained as an crystalline solid.

m.p.: 205°C dec.

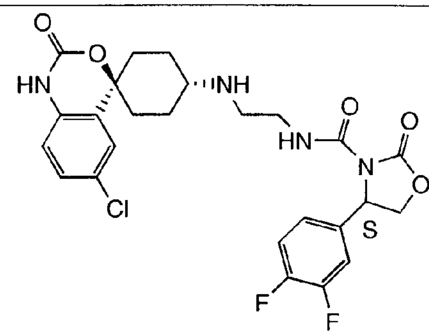
Analysis calc'd for C25H25ClF2N4O5•HCl•0.25 H2O:

C,52.13; H,4.64; N, 9.73

Found: C,52.11; H,4.78; N, 9.77

EXAMPLE 46

3-{[2-(*trans*-6-Chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one Hydrochloride (**46**)



The title compound was prepared according to the procedure described in Example 1, Step 3 except *trans*-1'-(2-aminoethylamino)-6-chloro-spiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-one from Example 45, Step 2, was substituted for 1'-(3-aminopropyl)-spiro[1H-indeno-1,4'-piperidine]. The hydrochloride salt was obtained as an crystalline solid.

m.p.: 197°C dec.

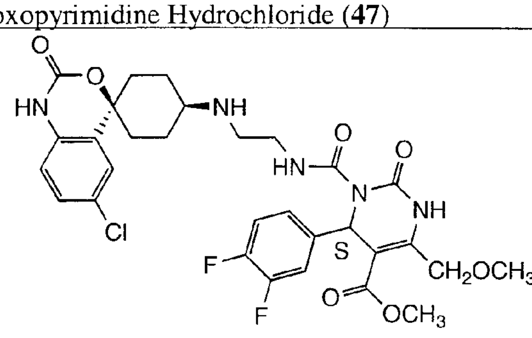
Analysis calc'd for C25H25ClF2N4O5•HCl:

C,52.55; H,4.59; N, 9.81

Found: C,52.33; H,4.51; N, 9.70

EXAMPLE 47

1-{[2-(*cis*-6-Chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride (**47**)



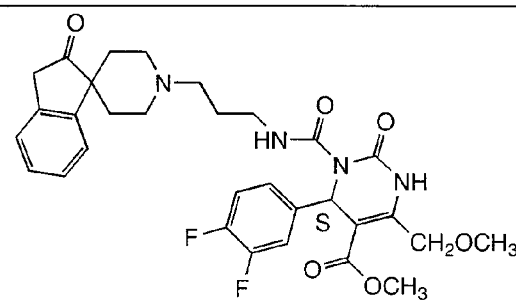
The title compound was prepared according to the procedure described in Example 1, Step 3 except *cis*-1'-(2-aminoethylamino)-6-chloro-spiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-one from Example 45, Step 2 was substituted for 1'-(3-aminopropyl)-spiro[1H-indeno-1,4'-piperidine], and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one. The hydrochloride salt was obtained as an amorphous solid.

Analysis calc'd for C30H32ClF2N5O7•HCl•0.55 H2O:

	C,51.88; H,4.95; N, 10.08
Found:	C,51.85; H,4.97; N, 10.37

EXAMPLE 48

<u>1-{[3-(2,3-Dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine (**48**)</u>



<u>Step 1</u>: 1'-t-Butoxycarbonyl- 2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one

A solution of m-chloroperbenzoic acid (80%, 2.2 gm, 10 mmol) in chloroform (20 mL) was added to a solution of 1'-t- butylcarbonylspiro[1H-indeno-1,4'-piperidine] (2.0 gm, 7 mmol) in chloroform((30 mL) containing powdered potassium carbonate (6.5 gm). This mixture was stirred at r.t. for 24 to 48 hours monitoring the reaction progress by TLC. Additional peracid was added if needed. The mixture was diluted with ethyl acetate and the organic layer washed with aq. sodium carbonate and water, dried and the solvent evaporated under vacuum. The crude 1'-t-butoxycarbonyl-2,3-epoxy-2,3 dihydro-spiro[1H-indeno-1,4'-piperidin]-

2(3H)-one was dissolved in methylene chloride (25 mL) and four drops of boron trifluoride etherate was added to catalyze the epoxide rearrangement. After stirring for one hour, the solution was washed with aq. sodium carbonate and the solvent evaporated. The residue was chromatographed on a silica gel column eluting with a 5 –15% ethyl acetate/hexane gradient to give the title compound as a solid which crystallized from cold hexane.

m.p.: 80-82°C.

Step 2: 2,3-Dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one

A solution of 1'-t-butoxycarbonyl- 2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)one (212 mg, 0.7 mmol) in chloroform (5 mL) containing trifluoroacetic acid (0.2 mL) was stirred at r.t. for 15 hours. The reaction mixture was washed with aq. sodium carbonate and the organic layer dried, filtered and evaporated to give the title compound as an oil which was used as is.

Step 3: 1-{[3-(2,3-Dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine

The title compound was prepared according to the procedure described in Example 1 except 2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one was substituted for spiro[1H-indeno-1,4'-piperidine] in Step 1 thereof, and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in Step 3. The freebase was obtained as an amorphous solid.

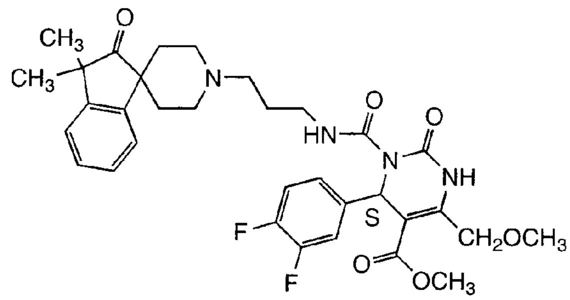
Analysis calc'd for $C_{31}H_{34}F_2N_4O_6 \cdot 0.25\ H_2O$:

C,61.93; H,5.78; N, 9.32

Found: C,61.96; H,5.78; N, 9.18

EXAMPLE 49

<u>1-{[3-(2,3-Dihydro-3,3-dimethyl-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine Hydrochloride (**49**)</u>



Step 1: 1'-t-Butoxycarbonyl- 2,3-dihydro-3,3-dimethyl-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one

A solution of 1'-t-butoxycarbonyl- 2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one (240 mg, 0.8 mmol) in dry dimethylformamide (1.5 mL) containing methyl iodide (0.50 mL, 8 mmol) and powdered cesium carbonate (540 mg, 1.65 mmol) was stirred at r.t. for fifteen hours under an argon atmosphere. This mixture was diluted with diethyl ether and the organic layer washed with water, dried and the solvent evaporated under vacuum. The crude product was used as is in the next step.

Step 2: 2,3-Dihydro-3,3-dimethylspiro[1H-indeno-1,4'-piperidin]-2(3H)-one

A solution of 1'-t-butoxycarbonyl- 2,3-dihydro-3,3-dimethyl-spiro[1H-indeno-1,4'-piperidin]-2(3H)one (262 mg, 0.8 mmol) in methylene chloride (8 mL) containing trifluoroacetic acid (1 mL) was stirred at r.t. for 3 hours. The reaction was washed with aq. sodium carbonate and the organic layer dried, filtered and evaporated to give the title compound as an oil (142 mg, 78% yield) which was used as is.

Step 3: 1-{[3-(2,3-Dihydro-3,3-dimethyl-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine Hydrochloride

The title compound was prepared according to the procedure described in Example 1 except 2,3-dihydro-3,3-dimethyl-spiro[1H-indeno-1,4'-piperidin]-2(3H)-one was substituted for spiro[1H-indeno-1,4'-piperidine] in Step 1, and (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6(S)-(3,4-difluorophenyl)-1-(4-nitrophenyloxycarbonyl)-pyrimidine was substituted for (+)-

4(S)-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-oxazolidin-2-one in Step 3. The hydrochloride salt was obtained as an amorphous solid.

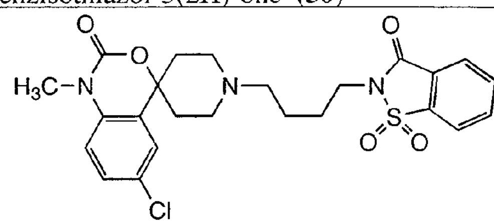
Analysis calc'd for C33H38F2N4O5•HCl•0.85 H2O:

C,58.59; H,6.06; N, 8.28

Found: C,58.60; H,5.94; N, 8.19

EXAMPLE 50

1,1-Dioxido-2-[4-(1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one **(50)**



The title compound was prepared according to the procedure described in Example 1, Step 1 except 1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one, which was prepared by methylation of the Boc-protected analog with methyl iodide and followed by deprotection with an acid (see Scheme 13),was substituted for spiro[1H-indeno-1,4'-piperidine] and 1,1-dioxido-2-(4-bromobutyl)-1,2-benzisothiazol-3(2H)-one was substituted for N-t-butoxy-carbonyl-3-bromopropylamine. The freebase was obtained as a crystalline solid.

m.p.: 170-171°C.

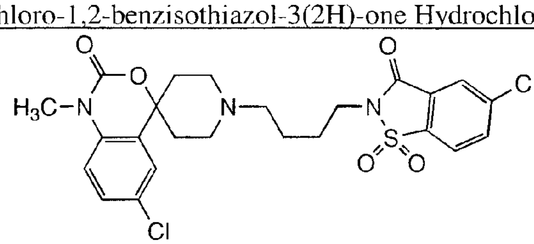
Analysis calc'd for C24H26ClN3O5S•0.50 H2O:

C,56.19; H,5.30; N, 8.19

Found: C,56.24; H,5.15; N, 8.07

EXAMPLE 51

1,1-Dioxido-2-[4-(1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-5-chloro-1,2-benzisothiazol-3(2H)-one Hydrochloride **(51)**



The title compound was prepared according to the procedure described in Example 1, Step 1 except 1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one, which was prepared by methylation of the Boc-protected analog with methyl iodide and followed by deprotection with an acid (see Scheme 13), was substituted for spiro[1H-indeno-1,4'-piperidine] and 1,1-dioxido-2-(4-bromobutyl)-5-chloro-1,2-benzisothiazol-3(2H)-one was substituted for N-t-butoxy-carbonyl-3-bromopropylamine. The hydrochloride salt was obtained as a crystalline solid. m.p.: 221-223°C.

Analysis calc'd for $C_{24}H_{25}Cl_2N_3O_5S$•HCl:

	C,50.14; H,4.56; N, 7.31
Found:	C,50.00; H,4.25; N, 7.34

EXAMPLE 52

As a specific embodiment of an oral composition, 100 mg of the compound **9** (Example 9) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

EXAMPLE 53

Screening assay: Alpha 1a Adrenergic Receptor Binding

Membranes prepared from the stably transfected human alpha 1a cell line (ATCC CRL 11140) were used to identify compounds that bind to the human alpha 1a adrenergic receptor. These competition binding reactions (total volume = 200 μl) contained 50 mM Tris-HCl pH. 7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [^{125} I]-HEAT, membranes prepared from the alpha 1a cell line and increasing amounts of unlabeled ligand. Reactions were incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C glass fiber filters with a Inotec 96 well cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined (Ki).

EXAMPLE 54

Selective Binding assays

Membranes prepared from stably transfected human alpha 1d and alpha 1b cell lines (ATCC CRL 11138 and CRL 11139, respectively) were used to identify compounds that selectively bind to the human alpha 1a adrenergic receptor.

These competition binding reactions (total volume = 200 μl) contained 50 mM Tris-HCl pH. 7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [^{125}I]-HEAT, membranes prepared from cell lines transfected with the respective alpha 1 subtype expression plasmid and increasing amounts of unlabeled ligand. Reactions were incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C glass fiber filters with a Inotec 96 well cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined (Ki).

All of the compounds of the present invention prepared in Examples 1-51 were found to have alpha 1a Ki values of less than about 127 nM, as determined via the screening assay described in Example 53. The following compounds were found to have alpha 1a Ki values of less than about 20 nM: **1**-**6**, **8**-**20**, **22**-**29**, **32**-**35** and **41**-**51**.

All of the compounds exhibited selectivity for the alpha 1a receptor with respect to both the alpha 1b and alpha 1d receptors. The following compounds were found to be at least about 10-fold more selective in binding to alpha 1a receptors versus binding to the alpha 1b and alpha 1d receptors: **1**-**29**, **33**, **34**, **41**, **42** and **44**-**51**.

The following compounds were found to have alpha 1a Ki values of less than about 10 nM and also found to be at least about 40-fold more selective in binding to alpha 1a receptors versus binding to the alpha 1b and alpha 1d receptors: **1**, **3-5**, **8-14**, **17-20**, **22**, **23**, **25-29**, **33**, **34**, **41**, **48** and **49**.

EXAMPLE 55

Counterscreen: Histamine-1 Selectivity

The binding affinity (Ki in nM) of the compounds of the present invention for histamine H1 receptors can determined via the binding assay described in Chang et al., *J. Neurochem.* (1979), 32: 1653, or as described in US 5403847, or suitable modifications thereof known to those skilled in the art. The assay can be used to eliminate agents which specifically affect binding to hH1 receptors.

EXAMPLE 56

Exemplary Counter Screens

1. Assay Title: Dopamine D2, D3, D4 in vitro screen

Objective of the Assay:

The objective of this assay is to eliminate agents which specifically affect binding of [3H] spiperone to cells expressing human dopamine receptors D2, D3 or D4.

Method:

Modified from VanTol et al., *Nature* (1991), 350: 610-613.

Frozen pellets containing specific dopamine receptor subtypes stably expressed in clonal cell lines are lysed in 2 ml lysing buffer (10mM Tris-HCl/5mM Mg, pH 7.4). Pellets obtained after centrifuging these membranes (15' at 24,450 rpm) are resuspended in 50mM Tris-HCl pH 7.4 containing EDTA, MgCl[2], KCl, NaCl, CaCl[2] and ascorbate to give a 1 Mg/mL suspension. The assay is initiated by adding 50-75 μg membranes in a total volume of 500 μl containing 0.2 nM [3H]-spiperone. Non-specific binding is defined using 10 μM apomorphine. The assay is terminated after a 2 hour incubation at room temperature by rapid filtration over GF/B filters presoaked in 0.3% PEI, using 50mM Tris-HCl pH 7.4.

2. Assay Title: Serotonin 5HT1a

Objective of the Assay

The objective of this assay is to eliminate agents which specifically affect binding to cloned human 5HT1a receptor

Method:

Modified from Schelegel and Peroutka, *Biochemical Pharmacology* (1986), 35: 1943-1949.

Mammalian cells expressing cloned human 5HT1a receptors are lysed in ice-cold 5 mM Tris-HCl, 2 mM EDTA (pH 7.4) and homogenized with a polytron homogenizer. The homogenate is centrifuged at 1000Xg for 30', and then the supernatant is centrifuged again at 38,000Xg for 30'. The binding assay contains 0.25

nM [3H]8-OH-DPAT (8-hydroxy-2-dipropylamino-1,2,3,4-tetrahydronaphthalene) in 50 mM Tris-HCl, 4 mM CaCl2 and 1mg/ml ascorbate. Non-specific binding is defined using 10 μM propranolol. The assay is terminated after a 1 hour incubation at room temperature by rapid filtration over GF/Cfilters

EXAMPLE 57

Exemplary Functional Assays

In order to confirm the specificity of compounds for the human alpha 1a adrenergic receptor and to define the biological activity of the compounds, the following functional tests may be performed:

1. In vitro Rat, Dog and Human Prostate and Dog Urethra

Taconic Farms Sprague-Dawley male rats, weighing 250-400 grams are sacrificed by cervical dislocation under anesthesia (methohexital; 50 mg/kg, i.p.). An incision is made into the lower abdomen to remove the ventral lobes of the prostate. Each prostate removed from a mongrel dog is cut into 6-8 pieces longitudinally along the urethra opening and stored in ice-cold oxygenated Krebs solution overnight before use if necessary. Dog urethra proximal to prostate is cut into approximately 5 mm rings, the rings are then cut open for contractile measurement of circular muscles. Human prostate chips from transurethral surgery of benign prostate hyperplasia are also stored overnight in ice-cold Krebs solution if needed.

The tissue is placed in a Petri dish containing oxygenated Krebs solution [NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; KH_2PO_4, 1.2 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 2.0 mM; dextrose, 11 mM] warmed to 37°C. Excess lipid material and connective tissue are carefully removed. Tissue segments are attached to glass tissue holders with 4-0 surgical silk and placed in a 5 ml jacketed tissue bath containing Krebs buffer at 37°C, bubbled with 5% CO_2/95% O_2. The tissues are connected to a Statham-Gould force transducer; 1 gram (rat, human) or 1.5 gram (dog) of tension is applied and the tissues are allowed to equilibrate for one hour. Contractions are recorded on a Hewlett-Packard 7700 series strip chart recorder.

After a single priming dose of 3 μM (for rat), 10 μM (for dog) and 20 μM (for human) of phenylephrine, a cumulative concentration response curve to an agonist is generated; the tissues are washed every 10 minutes for one hour. Vehicle or

antagonist is added to the bath and allowed to incubate for one hour, then another cumulative concentration response curve to the agonist is generated.

EC_{50} values are calculated for each group using GraphPad Inplot software. pA_2 (-log K_b) values were obtained from Schild plot when three or more concentrations were tested. When less than three concentrations of antagonist are tested, K_b values are calculated according

to the following formula $K_b = \frac{[B]}{x-1}$,

where x is the ratio of EC_{50} of agonist in the presence and absence of antagonist and [B] is the antagonist concentration.

2. Measurement of Intra-Urethral Pressure in Anesthetized Dogs

PURPOSE: Benign prostatic hyperplasia causes a decreased urine flow rate that may be produced by both passive physical obstruction of the prostatic urethra from increased prostate mass as well as active obstruction due to prostatic contraction. Alpha adrenergic receptor antagonists such as prazosin and terazosin prevent active prostatic contraction, thus improve urine flow rate and provide symptomatic relief in man. However, these are non-selective alpha 1 receptor antagonists which also have pronounced vascular effects. Because we have identified the alpha 1a receptor subtype as the predominent subtype in the human prostate, it is now possible to specifically target this receptor to inhibit prostatic contraction without concomitant changes in the vasculature. The following model is used to measure adrenergically mediated changes in intra-urethral pressure and arterial pressure in anesthetized dogs in order to evaluate the efficacy and potency of selective alpha adrenergic receptor antagonists. The goals are to: 1) identify the alpha 1 receptor subtypes responsible for prostatic/urethral contraction and vascular responses, and 2) use this model to evaluate novel selective alpha adrenergic antagonists. Novel and standard alpha adrenergic antagonists may be evaluated in this manner.

METHODS: Male mongrel dogs (7-12 kg) are used in this study. The dogs are anesthetized with pentobarbital sodium (35 mg/kg, i.v. plus 4 mg/kg/hr iv infusion). An endotracheal tube is inserted and the animal ventilated with room air using a Harvard instruments positive displacement large animal ventilator. Catheters (PE

240 or 260) are placed in the aorta via the femoral artery and vena cava via the femoral veins (2 catheters, one in each vein) for the measurement of arterial pressure and the administration of drugs, respectively. A supra-pubic incision ~1/2 inch lateral to the penis is made to expose the urethers, bladder and urethra. The urethers are ligated and cannulated so that urine flows freely into beakers. The dome of the bladder is retracted to facilitate dissection of the proximal and distal urethra. Umbilical tape is passed beneath the urethra at the bladder neck and another piece of umbilical tape is placed under the distal urethra approximately 1-2 cm distal to the prostate. The bladder is incised and a Millar micro-tip pressure transducer is advanced into the urethra. The bladder incision is sutured with 2-0 or 3-0 silk (purse-string suture) to hold the transducer. The tip of the transducer is placed in the prostatic urethra and the position of the Millar catheter is verified by gently squeezing the prostate and noting the large change in urethral pressure.

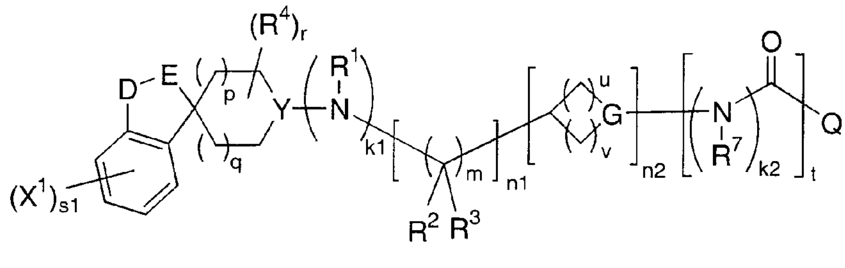
Phenylephrine, an alpha 1 adrenergic agonist, is administered (0.1-100 ug/kg, iv; 0.05 ml/kg volume) in order to construct dose response curves for changes in intra-urethral and arterial pressure. Following administration of increasing doses of an alpha adrenergic antagonist (or vehicle), the effects of phenylephrine on arterial pressure and intra-urethral pressure are re-evaluated. Four or five phenylephrine dose-response curves are generated in each animal (one control, three or four doses of antagonist or vehicle). The relative antagonist potency on phenylephrine induced changes in arterial and intra-urethral pressure are determined by Schild analysis. The family of averaged curves are fit simultaneously (using ALLFIT software package) with a four paramenter logistic equation constraining the slope, minimum response, and maximum response to be constant among curves. The dose ratios for the antagonist doses (rightward shift in the dose-response curves from control) are calculated as the ratio of the ED_{50}'s for the respective curves. These dose-ratios are then used to construct a Schild plot and the Kb (expressed as ug/kg, iv) determined. The Kb (dose of antagonist causing a 2-fold rightward shift of the phenylephrine dose-response curve) is used to compare the relative potency of the antagonists on inhibiting phenylephrine responses for intra-urethral and arterial pressure. The relative selectivity is calculated as the ratio of arterial pressure and intra-urethral pressure Kb's. Effects of the alpha 1 antagonists on baseline arterial pressure are also monitored. Comparison of the relative antagonist potency on changes in arterial pressure and intra-urethral pressure provide insight as to whether the alpha receptor subtype responsible for increasing intra-urethral pressure is also present in the

systemic vasculature. According to this method, one is able to confirm the selectivity of alpha 1a adrenergic receptor antagonists that prevent the increase in intra-urethral pressure to phenylephrine without any activity at the vasculature.

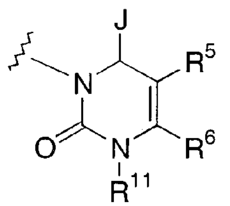
While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

WHAT IS CLAIMED IS:

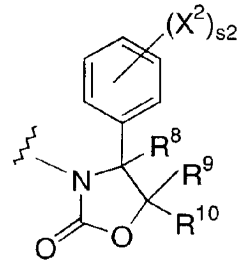
1. A compound of formula:



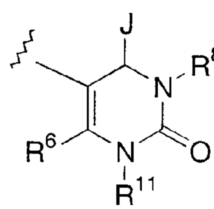
wherein Q is



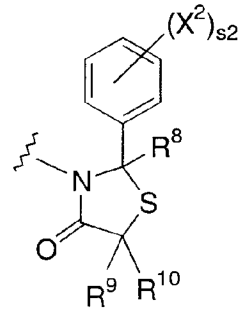
(q1),



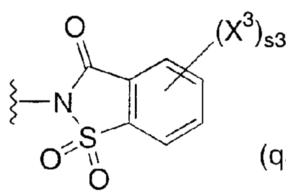
(q2),



(q3),



(q4), or



(q5)

;

D is absent, $[C(R^aR^b)]_{1-4}$, $O[C(R^aR^b)]_{1-2}$, $[C(R^aR^b)]_{1-2}O$, $C(R^a)=C(R^b)$, $C(R^aR^b)-C(R^a)=C(R^b)$, or $C(R^a)=C(R^b)-C(R^aR^b)$;

E is absent, $C(=O)$, $C(=O)O$, $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$, or $N(R^c)C(=O)O$, provided that (i) when E is absent, D is $[C(R^aR^b)]_{2-4}$, $O[C(R^aR^b)]_{1-2}$, $[C(R^aR^b)]_{1-2}O$, $C(R^a)=C(R^b)$, $C(R^aR^b)-C(R^a)=C(R^b)$, or $C(R^a)=C(R^b)-C(R^aR^b)$; (ii) when E is $C(=O)$ or $C(=O)O$, D is $C(R^aR^b)$ or $C(R^aR^b)C(R^aR^b)$; and (iii) when E is $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$ or $N(R^c)C(=O)O$, D is absent or $C(R^aR^b)$;

G is CH or N;

Y is CH or N;

k1 is an integer which is equal to zero when Y is N, and is equal to 1 when Y is CH;

k2 is an integer which is equal to zero when n2 is 1 and G is N, and is equal to 1 when (i) n2 is 1 and G is CH or (ii) n2 is zero;

m is an integer from 2 to 6;

n1 and n2 are each integers equal to zero or 1, with the proviso that the sum of n1 and n2 is 1 or 2;

p and q are each independently integers from zero to 3;

r is an integer from zero to 4;

R^1 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $(CH_2)_{1-4}CF_3$, $(CH_2)_{0-4}CO_2R^e$, $(CH_2)_{0-4}C(=O)N(R^e)_2$, $(CH_2)_{0-4}C(=O)R^e$, $(CH_2)_{2-4}OR^d$, $(CH_2)_{1-4}CF_3$, $(CH_2)_{0-4}SO_2R^e$, $(CH_2)_{0-4}SO_2N(R^e)_2$ or $(CH_2)_{1-4}CN$;

R^2 and R^3 are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

each R^4 is a substituent connected to a ring atom other than spiro substituted carbon or Y and is independently hydrogen or C_1-C_4 alkyl;

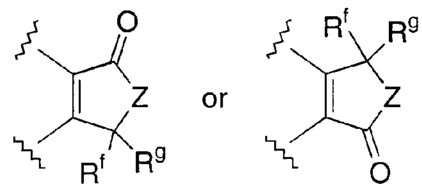
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $(CH_2)_{0\text{-}4}C(=O)R^d$, $(CH_2)_{0\text{-}4}CN$, $(CH_2)_{0\text{-}4}CF_3$, $(CH_2)_{0\text{-}4}CO_2R^e$, $(CH_2)_{0\text{-}4}C(=O)N(R^e)_2$, $(CH_2)_{0\text{-}4}SO_2R^d$ or $(CH_2)_{0\text{-}4}SO_2N(R^e)_2$;

R^6 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $(CH_2)_{1\text{-}4}OR^d$ or $(CH_2)_{0\text{-}4}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:

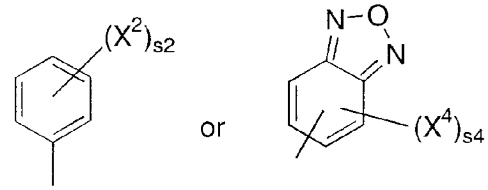


wherein Z is O or NR^f;

R^8 and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}4}CF_3$;

R^9 and R^{10} are each independently hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $(CH_2)_{2\text{-}4}OR^c$ or $(CH_2)_{0\text{-}4}CF_3$; or one of R^9 and R^{10} is hydrogen and the other of R^9 and R^{10} is $(CH_2)_{0\text{-}4}CO_2R^e$ or $(CH_2)_{0\text{-}4}C(=O)N(R^e)_2$;

J is



;

each X^1 is independently hydrogen, halogen, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_8 cycloalkyl, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{0-4}C(=O)N(R^h)_2$, C_1-C_6 alkoxy, fluorinated C_1-C_6 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_8 cycloalkyl, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{0-4}C(=O)N(R^h)_2$, C_1-C_6 alkoxy, fluorinated C_1-C_6 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl;

each X^3 is independently hydrogen, halogen, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_8 cycloalkyl, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{0-4}C(=O)N(R^h)_2$, C_1-C_6 alkoxy, fluorinated C_1-C_6 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl;

each X^4 is independently hydrogen, halogen, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, fluorinated C_1-C_6 alkyl, fluorinated C_3-C_8 cycloalkyl, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{0-4}C(=O)N(R^h)_2$, C_1-C_6 alkoxy, fluorinated C_1-C_6 alkoxy, C_2-C_8 alkoxyalkyl, or fluorinated C_2-C_8 alkoxyalkyl;

R^a and R^b are each independently hydrogen, C_1-C_4 alkyl, or fluorinated C_1-C_4 alkyl;

R^c is hydrogen, C_1-C_4 alkyl, or fluorinated C_1-C_4 alkyl;

R^d is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or $(CH_2)_{0-4}CF_3$;

R^e is hydrogen, C_1-C_6 alkyl, C_4-C_8 cycloalkyl, or $(CH_2)_{1-4}CF_3$;

R^f and R^g are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

R^h is hydrogen, C_1-C_4 alkyl, or fluorinated C_1-C_4 alkyl;

s1 is an integer from zero to 4;

s2 is an integer from zero to 5;

s3 is an integer from zero to 4;

s4 is an integer from zero to 3;

t is an integer which is zero or 1; and

u and v are independently integers from 1 to 3;

and further provided that

(i) when Q is (q1), k1 is zero, and n2 is zero, then (1) E is C(=O) and D = $C(R^aR^b)$, or (2) E is $N(SO_2R^c)C(R^aR^b)$ or $N(R^c)C(=O)O$;

(ii) when Q is (q3), then t is 1;

(iii) when Q is (q5), then (1) t is zero and (2) G is CH when n2 is 1; and

(iv) when Q is (q1), (q2), or (q4), n2 is 1, and G is N, then t is 1;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein

p and q are each integers from zero to 3, provided that the sum of p and q is an integer less than or equal to 3;

r is an integer from zero to 2;

R^1 and R^7 are each independently hydrogen, C_1-C_6 alkyl, or $(CH_2)_{1-4}CF_3$;

one of R^2 and R^3 is hydrogen and the other of R^2 and R^3 is hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

R^a and R^b are each independently hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0-4}CF_3$;

R^c is hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0-4}CF_3$;

R^d is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or $(CH_2)_{0-2}CF_3$;

R^e is hydrogen, C_1-C_4 alkyl, C_4-C_6 cycloalkyl, or $(CH_2)_{1-2}CF_3$;

R^f and R^g are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^h is hydrogen, C_1-C_4 alkyl, or $(CH_2)_{0-4}CF_3$;

s1 is an integer from zero to 2;

s2 is an integer from zero to 3;

s3 is an integer from zero to 2;

s4 is an integer from zero to 2;

u is an integer from 1 to 2; and

v is an integer from 1 to 3;

and further provided that

(i) when Q is (q1), k1 is zero, and n2 is zero, then (1) E is C(=O) and D = $C(R^aR^b)$, or (2) E is $N(SO_2R^c)C(R^aR^b)$ or $N(R^c)C(=O)O$;

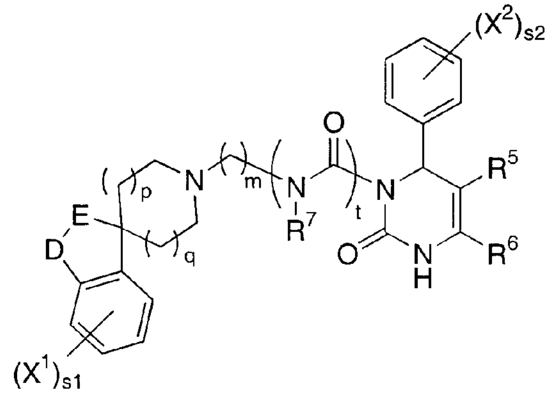
(ii) when Q is (q3), then t is 1;

(iii) when Q is (q5), then (1) t is zero and (2) G is CH when n2 is 1; and

(iv) when Q is (q1), (q2), or (q4), n2 is 1, and G is N, then t is 1;

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 2, wherein the compound is of formula:



;

wherein

D is absent or $[C(R^aR^b)]$; and

E is $C(=O)$, $N(SO_2R^c)C(R^aR^b)$, or $N(R^c)C(=O)O$, provided that when E is $C(=O)$, D is $[C(R^aR^b)]$;

or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 3, wherein E is $N(SO_2R^c)C(R^aR^b)$ or $N(R^c)C(=O)O$;

or a pharmaceutically acceptable salt therof.

5. The compound according to claim 4, wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

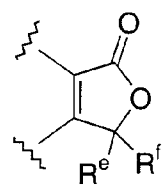
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $C(=O)R^d$, $(CH_2)_{0\text{-}2}CO_2R^e$, $(CH_2)_{0\text{-}2}C(=O)N(R^e)_2$, or SO_2R^d;

R^6 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{1\text{-}3}OR^d$ or $(CH_2)_{0\text{-}3}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:



;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$; and

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 4, selected from the group consisting of

(+/-)-1-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine;

(+/-)-1-{5-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine;

(+/-)-1-{[3-(6-Fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine;

(+/-)-1-{5-(6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[3-(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[3-(1,2-dihydro-1-methanesulfonyl-6-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[3-(2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine;

1-{[3-(2,3-dihydro-3,3-dimethyl-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]amino-carbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxo-pyrimidine;

and pharmaceutically acceptable salts thereof.

7. The compound according to claim 2, wherein

Q is (q2); and

Y is N;

and further provided that when n2 is 1 and G is N, then t is 1;

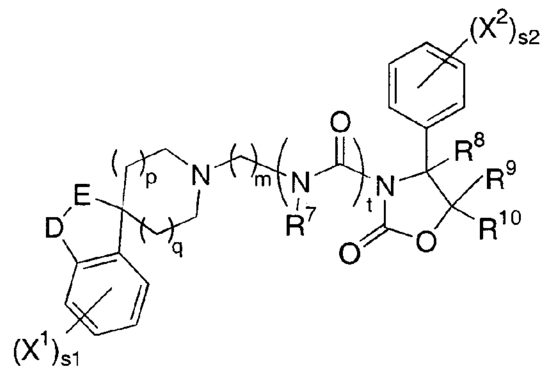
or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 7, wherein the compound is

3-{[3(R/S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

or a pharmacutically acceptable salt thereof.

9. The compound according to claim 7, wherein the compound is of formula:



;

or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 9, wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

R^8 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2-4}OR^d$ or $(CH_2)_{0-2}CF_3$;

R^9 and R^{10} are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2-4}OR^d$ or $(CH_2)_{0-2}CF_3$; or one of R^9 and R^{10} is hydrogen and the other of R^9 and R^{10} is CO_2R^e or $C(=O)N(R^e)_2$;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$; and

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10, selected from the group consisting of

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(6-fluorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)pentyl}-4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-5(S)-methoxycarbonyl-oxazolidin-2-one;

3-{[3-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-5(S)-aminocarbonyl-oxazolidin-2-one;

3-{[3-(spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

1-{[3-(5-monochloro-spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

1-{[3-(6-monochloro-spiro[1H-indeno-1,4'-piperidin]-1'-yl)propyl]amino-carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(spiro[1H-indano-1,4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{5-(spiro[1H-indeno-1,4'-piperidin]-1'-yl)pentyl }-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

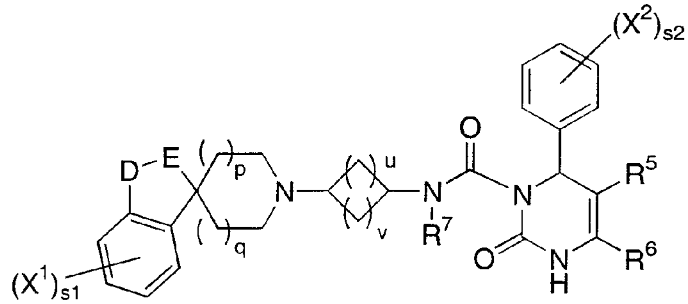
3-{[3-(6-chloro-spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(6-fluoro-spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[3-(2,3-dihydro-spiro[1H-indeno-1,4'-piperidin]-2(3H)-on-1'-yl)propyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

and pharmaceutically acceptable salts thereof.

12. The compound according to claim 2, wherein the compound is of formula:



or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 12, wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

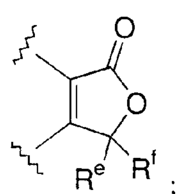
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $C(=O)R^d$, $(CH_2)_{0-2}CO_2R^e$, $(CH_2)_{0-2}C(=O)N(R^e)_2$, or SO_2R^d;

R^6 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{1-3}OR^d$ or $(CH_2)_{0-3}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:



each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2; and

u and v are independently integers equal to 1 or 2;

or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 13, selected from the group consisting of

1-{*cis*-[3(S)-(spiro[indano-1,4'-piperidin]-1'-yl)cyclopent-1(R)-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{*trans*-[3(R)-(spiro[indano-1,4'-piperidin]-1'-yl)cyclopent-1(R)-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[*cis*-[3(S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclopent-1(R)-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[*trans*-[3(R)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclopent-1(R)-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

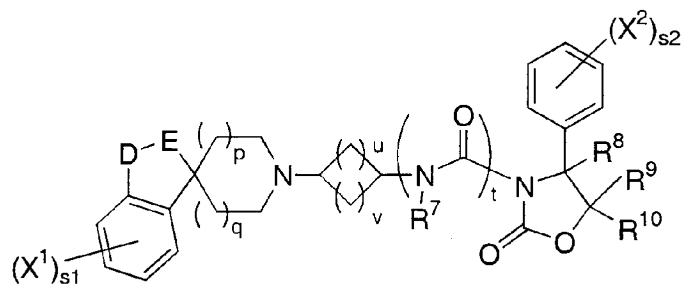
1-{[*cis*-3-(spiro[indano-1,4'-piperidin]-1'-yl)cyclobut-1-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

1-{[*trans*-3-(spiro[indano-1,4'-piperidin]-1'-yl)cyclobut-1-yl]aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

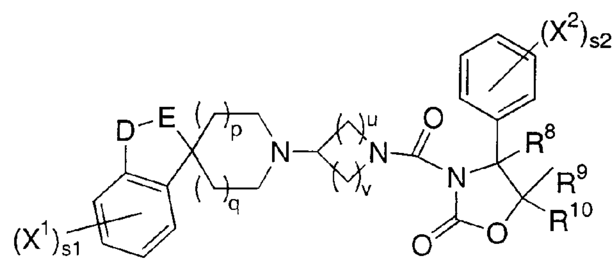
1-{[*trans*-4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl) cyclohex-1-yl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

and pharmaceutically acceptable salts thereof.

15. The compound according to claim 2, wherein the compound is of formula:



or



;

or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 15, wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

R^8 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$;

R^9 and R^{10} are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$; and

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 16, selected from the group consisting of

3-{[*cis*-3(S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[*trans*-3(R)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[*trans*-4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[*cis*-4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclohex-1-yl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one ;

(3-{*trans*-4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)cyclohex-1-yl}- 4(R/S)-(3,4-difluorophenyl)-oxazolidin-2-one ;

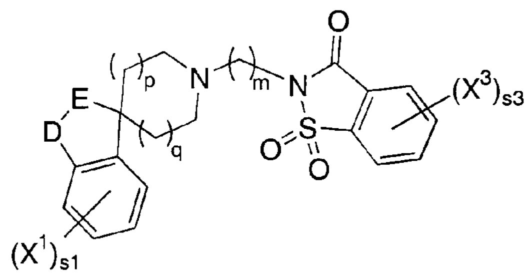
3-{[4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-piperidin-1-yl]carbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one ;

3-{*cis/trans*-3(R/S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(S)-yl}- 4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{*cis/trans*-3(R/S)-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)-cyclopent-1(R)-yl}- 4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

and pharmaceutically acceptable salts thereof.

18. The compound according to claim 2, wherein the compound is of formula:



;

or a pharmaceutically acceptable salt thereof.

19. The compound according to claim 18, wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

each X^3 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$;

m is an integer equal to 4; and

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;
or a pharmaceutically acceptable salt thereof.

20. The compound according to claim 19, selected from the group consisting of

1,1-dioxido-2-[4-(spiro[indano-1,4'-piperidin]-1'-yl)butyl]-5-chloro-1,2-benzisothiazol-3(2H)-one;

1,1-dioxido-2-[4-(2,3-dihydrospiro[1H-indeno-1,4'-piperidin]-2(3H)on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one;

1,1-dioxido-2-[4-(6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one;

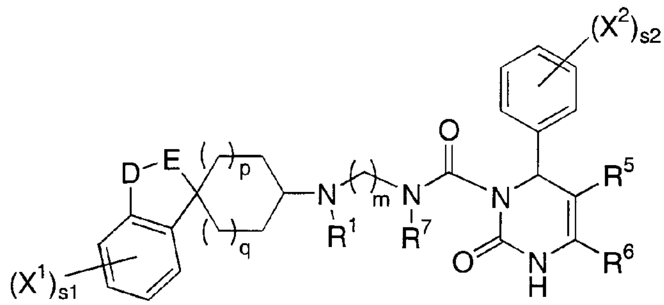
1,1-dioxido-2-[4-(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one;

1,1-dioxido-2-[4-(1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-1,2-benzisothiazol-3(2H)-one;

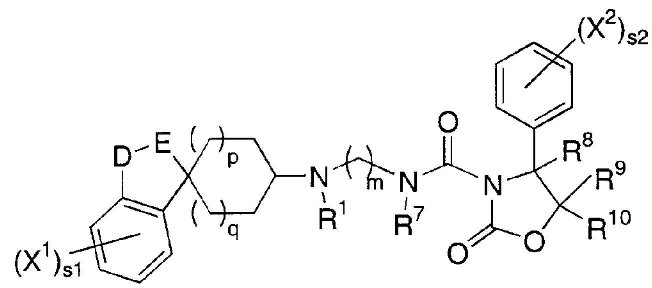
1,1-dioxido-2-[4-(1-methyl-6-chlorospiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-on-1'-yl)butyl]-5-chloro-1,2-benzisothiazol-3(2H)-one;

and pharmaceutically acceptable salts thereof.

21. The compound according to claim 2, wherein the compound is of formula:



or



;

wherein

D is absent, $[C(R^aR^b)]_{1-4}$, $O[C(R^aR^b)]_{1-2}$, $[C(R^aR^b)]_{1-2}O$, $C(R^a)=C(R^b)$, $C(R^aR^b)-C(R^a)=C(R^b)$, or $C(R^a)=C(R^b)-C(R^aR^b)$; and

E is absent, C(=O), C(=O)O, $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$, or $N(R^c)C(=O)O$, provided that (i) when E is absent, D is $[C(R^aR^b)]_{2-4}$, $O[C(R^aR^b)]_{1-2}$, $[C(R^aR^b)]_{1-2}O$, $C(R^a)=C(R^b)$, $C(R^aR^b)-C(R^a)=C(R^b)$, or $C(R^a)=C(R^b)-C(R^aR^b)$; (ii) when E is C(=O) or C(=O)O, D is $C(R^aR^b)$ or $C(R^aR^b)C(R^aR^b)$; and (iii) when E is $N(SO_2R^c)C(R^aR^b)$, $N(R^c)C(=O)$ or $N(R^c)C(=O)O$, D is absent or $C(R^aR^b)$;

or a pharmaceutically acceptable salt thereof.

22. The compound according to claim 22, wherein

each X^1 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0-4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0-4}CO_2R^h$, $(CH_2)_{1-4}OCH_3$, or $(CH_2)_{1-4}OCF_3$;

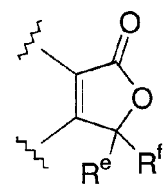
R^5 and R^6 are defined as:

(A) R^5 is hydrogen, $C(=O)R^d$, $(CH_2)_{0-2}CO_2R^e$, $(CH_2)_{0-2}C(=O)N(R^e)_2$, or SO_2R^d;

R^6 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{1-3}OR^d$ or $(CH_2)_{0-3}CF_3$;

or

(B) R^5 and R^6 together with the carbons to which they are attached form a ring of formula:



;

R^8 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$;

R^9 and R^{10} are each independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_{2\text{-}4}OR^d$ or $(CH_2)_{0\text{-}2}CF_3$;

each X^2 is independently hydrogen, halogen, cyano, C_1-C_4 alkyl, $(CH_2)_{0\text{-}4}CF_3$, C_1-C_4 alkoxy, OCF_3, $(CH_2)_{0\text{-}4}CO_2R^h$, $(CH_2)_{1\text{-}4}OCH_3$, or $(CH_2)_{1\text{-}4}OCF_3$; and

m is an integer which is 2 or 3; and

p and q are each integers equal to zero or 1, provided that the sum of p and q is an integer equal to 1 or 2;

or a pharmaceutically acceptable salt thereof.

23. The compound according to claim 22, wherein

D is absent or $[C(R^aR^b)]_{1\text{-}2}$; and

E is C(=O), $N(SO_2R^c)C(R^aR^b)$, or $N(R^c)C(=O)O$, provided that when E is C(=O), D is $[C(R^aR^b)]_{1\text{-}2}$; and when E is $N(SO_2R^c)C(R^aR^b)$ or $N(R^c)C(=O)O$, D is absent or $C(R^aR^b)$;

24. The compound according to claim 23, selected from the group consisting of

3-{[2-(*cis*-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

3-{[2-(*trans*-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-4(S)-(3,4-difluorophenyl)-oxazolidin-2-one;

1-{[2-(*cis*-6-chlorospiro[4H-3,1-benzoxazine-4,4'-cyclohexan]-2(1H)-on-1'-yl)amino-ethyl]-aminocarbonyl}-5-methoxycarbonyl-4-methoxymethyl-6(S)-(3,4-difluorophenyl)-2-oxopyrimidine;

and pharmaceutically acceptable salts thereof.

25. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

26. A pharmaceutical composition made by combining a therapeutically effective amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

27. A process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

28. The composition according to claim 25 further comprising a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor.

29. The composition according to claim 28, wherein the testosterone 5-alpha reductase inhibitor is a type 1, a type 2, both a type 1 and a type 2, or a dual type 1 and type 2 testosterone 5-alpha reductase inhibitor.

30. The composition according to claim 29, wherein the testosterone 5-alpha reductase inhibitor is a type 2 testosterone 5-alpha reductase inhibitor.

31. The composition according to claim 30, wherein the testosterone 5-alpha reductase inhibitor is finasteride.

32. A method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1.

33. The method according to claim 32, wherein the compound does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperlasia.

34. The method according to claim 32, wherein the compound is administered in combination with a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor.

35. The method according to claim 34, wherein the testosterone 5-alpha reductase inhibitor is finasteride.

36. A method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering a therapeutically effective amount of the composition according to claim 32.

37. The method according to claim 36, wherein the composition further comprises a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor.

38. A method of relaxing lower urinary tract tissue in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1.

39. The method according to claim 38, wherein the compound is administered in combination with a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor.

40. The method according to claim 39, wherein the testosterone 5-alpha reductase inhibitor is finasteride.